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CLINICAL EXPERIENCE WITH SULFAPYRIDINE

A REPORT OF 33 CASES

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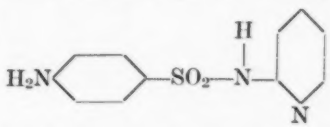
THE clinical success of sulfanilamide in infections with streptococci, gonococci, and meningococci has stimulated the search for new and related chemical compounds of therapeutic value. Of these numerous derivatives 2-para-amino-benzene-sulfanilamide-pyridine



has emerged as a valuable chemotherapeutic agent because of its effectiveness against pneumococci as well as the organisms affected by sulfanilamide. Whitby[1] first reported favorable results in the treatment of pneumococcal infections, and others have had similar success.[2-4] Successful therapy also has been reported in regard to meningococcal,[5] gonococcal,[6, 7] staphylococcal,[8] and streptococcal[9] infections.

The drug, which has been called by various names—sulfanilamide-pyridine, sulfone-pyridine, pyridine sulfanilamide compound, dagenan, M & B 693, finally named sulfapyridine by the Council on Pharmacy and Chemistry[10]—is a slightly bitter powder made up in 0.3 and 0.5 gm. tablets and capsules. It is given by mouth in either tablet or suspension, and also has been given intramuscularly in olive oil. It is said to be soluble 1:1,000. Evans and Gaisford[3] recommend the following dosage:

1-3 months	0.8 gm. daily
6-24 months	1.5 gm. daily
3 years	2.0 gm. daily
5 years	3.0 gm. daily

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TABLE I

PATIENTS WITH PNEUMOCOCCAL INFECTIONS TREATED WITH SULFAPYRIDINE

CASE NUMBER	AGE	DIAGNOSIS	ORGANISM	DAYS OF ILLNESS BEFORE TREATMENT	DOSAGE OF SULFAPYRIDINE, GM./DAY	DAYS OF TREATMENT	LEVEL OF SULFAPYRIDINE IN BLOOD, MG. PER CENT	TEMPERATURE RESPONSE*	W. B. C. RESPONSE*	RESULT	COMMENTS
1	18 mo.	Lobar pneumonia	Pneumococcus untypable	2	1.8	2	?	Fell from 40.5 to 37° C. in 24 hr. (105 to 99° F.)	Fell from 40,000 to 15,000	Well	Marked clinical improvement on first day. Vomited all during treatment. Crisis on third day.
2a	2 yr.	Lobar pneumonia	?	4	3.0	8	?	Fell from 40 to 37° C. in 60 hr. (104 to 98.6° F.)	Rose from 11,000 to 15,000	Improved	W.B.C. remained elevated and resolution slow on first admission. Symptoms recurred 8 days after drug was withdrawn. Readmitted for treatment with same dosage five days later. Response and resolution satisfactory. Vomiting, cyanosis and methemoglobin formation noted. Protocol below.
2b	2 yr.	Lobar pneumonia	Pneumococcus not typed	5	3.0	5	3.7	Fell from 41 to 37° C. in 28 hr. (106 to 98.6° F.)	Fell from 15,000 to 7,800	Well	
3	4 yr.	Lobar pneumonia	Pneumococcus untypable	5	1.2	6	0.8	Fell from 40 to 37° C. in 36 hr. (104 to 98.6° F.)	Fell from 14,000 to 7,000	Well	Right upper and middle lobes involved. Toxic signs disappeared rapidly. Vomited once during treatment. Two days' treatment with sulfanilamide without benefit.
4	3 yr.	Lobar pneumonia	Pneumococcus Type II	2	3.0	7	3.7	Fell from 39.8 to 37° C. in 36 hr. (103.6 to 98.6° F.)	Fell from 19,000 to 15,000	Well	Right upper lobe involved. Vomited once on second day of treatment. Resolution satisfactory.

*The first temperature reading and white blood cell count are those at the beginning of treatment. The last white blood count is that obtained when treatment was discontinued.

TABLE I—CONT'D

5	2 yr.	Lobar pneumonia	Pneumococcus Type II	4	2.0	6	†	Fell from 40 to 37° C. in 36 hr. (104 to 98.6° F.)	Fell from 26,000 to 18,000	Well	Right middle lobe involved. Recovery uneventful. Vomited once. No recurrence.
6	18 mo.	Lobar pneumonia	Pneumococcus untypable	1	1.8	3	†	Fell from 40.5 to 37° C. in 24 hr. (105 to 98.6° F.)	Fell from 31,000 to 13,000	Well	Signs of pneumonia appeared after admission for otitis media. Response to therapy immediate. No toxic signs.
7	10 yr.	Lobar pneumonia	Pneumococcus Type II	1	3.0	5	3.8 6.2	Fell from 40.5 to 37° C. in 48 hr. (105 to 98.6° F.)	Fell from 29,000 to 8,000	Well	Patient a known asthmatic. Recovery rapid and complete. Slight cyanosis.
8	9 mo.	Lobar pneumonia	Pneumococcus not typed	3	1.2	4	2.7	Fell from 39.6 to 37.2° C. in 48 hr. (103 to 99° F.)	Fell from 20,000 to 7,200	Well	Improvement rapid. Vomiting present before, during, and after treatment. Youngest case in group.
9	2 yr.	Pneumococcal bacteremia	Pneumococcus Type X	56	1.2 2.0 3.0	25 8 40	4.3 7.1 8.2	Fluctuated widely	Ranged from 22,000 to 7,200	Well	Three weeks on sulfanilamide without benefit. Condition controlled by sulfapyridine. See protocol below.
10	3 yr.	Nephrosis with peritonitis	Pneumococcus Type IX	1	1.8	3	2.0	Fell from 40.1 to 37° C. in 36 hr. (104 to 98.6° F.)	Rose from 25,000 to 26,000	Improved	Type IX pneumococcus from nose and throat after onset of symptoms. Much improvement noted, but hemoglobin fell from 104 to 62 per cent in 3 days, so drug was discontinued; 4 days later symptoms reappeared; and on 4th day of illness, sulfapyridine reinstituted with immediate recovery, and no change in hemoglobin level. No recurrence.
		Recurrence	Pneumococcus Type IX	4	1.2	4	2.2	Fell from 40.1 to 37° C. in 24 hr. (104 to 98.6° F.)	Fell from 25,000 to 7,800	Well	

TABLE I—CONT'D

CASE NUMBER	AGE	DIAGNOSIS	ORGANISM	DAYS OF ILLNESS BEFORE TREATMENT	DOSAGE OF SULFAPYRIDINE, GM./DAY	DAYS OF TREATMENT	LEVEL OF SULFAPYRIDINE IN BLOOD, MG. PER CENT	TEMPERATURE RESPONSE*	W. B. C. RESPONSE†	RESULT	COMMENTS
11	2 yr.	Mediastinitis	Pneumococcus Types I and II	21	2.0	14	?	Fell from 39 to 37° C. in 24 hr. (102.4 to 98.6° F.). Remained afebrile	Fell from 19,000 to 8,000	Well	Superior mediastinal abscess drained surgically, but fever remained high until sulfapyridine therapy started. Improvement rapid thereafter.
12	18 mo.	Empyema	Pneumococcus untypable	6	2.0	6	1.8	Fell from 39.4 to 36.8° C. in 48 hr. (103 to 98° F.)	Fell from 13,000 to 10,000	Well	Thoracotomy done prior to admission. Wound sutured, no further drainage. Recovery rapid thereafter.
13	7 yr.	Empyema	Pneumococcus Type I	?	3.0	5	4.7	Slight lowering and flattening of temperature	Fell from 15,000 to 5,000	Improved	Child had tuberculosis of spine and 4th right rib, followed by empyema of unknown duration. Fusospirochetes also found in empyema fluid. No pneumococci found in fluid after treatment, although drainage continued.

The following is a preliminary report on the use of sulfapyridine in 33 children in the Duke Hospital. The patients ranged in age from one week to thirteen years. Twenty-two were boys and 11 were girls. The conditions for which the children were treated are listed in Tables I, II and III. The patients have been divided into three groups: those with pneumococcal infections, those with bronchopneumonia, and a third, or miscellaneous, group.

The most successful results were obtained in thirteen pneumococcal infections (Table I). Eight of these patients had lobar pneumonia with symptoms from one to five days. All degrees of toxicity were present. Three of the patients had Type II infections, and in the others the organism was identified but could not be typed.*

All the patients showed marked improvement within forty-eight hours, regardless of the day of the disease on which treatment was begun. Temperatures usually reached normal in twenty to forty-eight hours with an average of thirty-six hours. The true crisis of lobar pneumonia was not seen but, rather, a rapid lysis. In general, the course of the pneumonic patient was one of marked improvement during the first day with relief of toxicity, malaise, and some fall in temperature. During the second day the appetite improved, headache and other symptoms disappeared, the white blood count fell, and the hemogram improved. Resolution usually began with the fall in temperature.

The following protocol represents at first an atypical and later a typical response to therapy.

CASE 2.—No. A 10159. A 2-year-old colored boy entered the hospital with a history of high fever, cough, vomiting, abdominal pain, and malaise for four days. Examination revealed moderate toxicity with signs of consolidation in the right lower lobe, confirmed by x-ray. The temperature was 40° C. (104° F.), pulse 136, respirations rapid and accompanied by grunting. White blood cells numbered 11,000, with marked shift to the left in the hemogram. The patient was immediately given sulfapyridine, 0.5 gm. every six hours, which was continued for ten days. His temperature fell from 40° to 37° C. (104° to 98.6° F.) in 60 hours, and there was marked improvement on the second and third days. The white blood cell count rose to 14,000, but there was a satisfactory shift to the right on differential count. According to physical signs and x-ray examination, resolution was delayed at the right base, but because of clinical improvement he was discharged. Eight days later his previous symptoms returned, accompanied by chills, earache, and vomiting. After five days he returned

*This is in accord with the experience of others who found that after treatment the organism seemed to lose the ability to react to typing serum. Whitby[1] feels that this is probably a specific reaction of the drug on the organism, while Fleming[2] thinks the decapsulation results from increased inhibitory power of the serum. In our experience, typability returns soon after the drug is discontinued (see Case 9).

to the hospital. Consolidation of the right middle and lower lobes was found. Sulfapyridine was again given in the same dosage, and continued for four days. The patient's temperature fell from 41° to 37° C. (106° to 98.6° F.) in twenty-eight hours, the white blood cells from 15,000 to 7,800 during this period, and resolution and clinical improvement were rapid. On his first visit, he vomited twice during therapy; on the second, traces of methemoglobin were found in his blood. Concentration of the drug in the blood was 3.7 mg. per cent on two occasions. No pneumococci were isolated on his first admission; on his second, an untypable pneumococcus was cultured from the nose and throat.

In addition to the eight cases of lobar pneumonia, five other patients with pneumococcal infections were treated with the drug. Case 10 was included with this group because of the frequency of pneumococcal peritonitis in patients with the nephrotic syndrome, and the appearance of a Type IX pneumococcus in the throat culture at the onset of the abdominal symptoms. The protocol below represents failure of sulfanilamide, and at least partial success with sulfapyridine.

Case 9.—No. A 7185. The patient was a 2-year-old white boy with a history of recurrent pneumonia for five weeks. Examination and x-ray showed an area at the left base which appeared to be unresolved pneumonia. Temperature was 37.2° C. (98.9° F.); white blood cell count, 15,000. On the fourth day he became flushed, hot, dyspneic, and appeared frightened. His temperature rose to 40° C. (104° F.). The blood culture showed a pneumococcus whose capsule reacted to Type X serum. He was given 1.8 gm. of sulfanilamide daily for twenty-one days but had four similar episodes, on the last of which the blood culture showed 50 colonies per cubic centimeter. For the following 24 days he received 1.2 gm. sulfapyridine daily with three minor episodes and one severe one. Blood cultures were negative except for one colony during the severe attack. He was taken from the hospital against advice but returned in three days after having had one of his worst episodes. Temperature was 40° C. (104° F.), the blood culture showed two colonies per cubic centimeter, Type X pneumococcus. For seven weeks he received 2 to 3 gm. daily except for five short periods when the drug was discontinued for two to six days, during every one of which his temperature rose and his blood culture became positive. Between bouts of fever his temperature was normal, and there were no toxic symptoms. Often the organism could not be typed with specific sera. After receiving a total of 143.6 gm. of sulfapyridine over a three months' period, it was discontinued without any flare-up, and he was discharged well. The blood concentration varied between 0.5 and 8.4 mg. per cent irrespective of the size of the dose. He was also given small amounts of Type X pneumococcus serum to

stimulate an antibody response. His titer rose from 1:40 to 1:160. Diagnosis: question of pneumococcal endocarditis.

The patient in Case 12 had uncomplicated pneumococcal empyema and responded well to treatment, but the patient in Case 13 failed to show any considerable improvement except for lowering of the temperature. She had, however, a mixed type of infection.

In all cases the ease of administration and the effectiveness of the tablets afforded relief from the tedious, but formerly necessary, procedures of emergency typing and identification of the organism; spared the patient such rigorous measures as gastric lavage, tracheal swabbing, or lung puncture; eliminated the risks of serum therapy; and gave him complete rest during the time when rest was most needed.

The results in children with bronchopneumonia (Table II) have not been so striking as those in group I. The patients were younger and the pulmonary involvement more widespread. Two patients (Cases 18 and 21) had received sulfanilamide without benefit but improved when sulfapyridine was instituted. In general, improvement was noted within two or three days after therapy was begun. The temperature fell to within normal limits during this time, and the process in the lung appeared to resolve with satisfactory rapidity. The success in a small number of cases treated does not permit definite conclusions but indicates that further use of sulfapyridine in bronchopneumonia is justified.

Table III represents a mixed group of eleven cases of which eight were apparently caused by hemolytic *Staphylococcus aureus*. The results were encouraging, but, again, not impressive. Significant comments on these cases are contained in the table.

In view of the fact that sulfapyridine is a bacteriostatic agent, it would seem probable that greater therapeutic action could be expected from the combined use of the drug and specific antisera. Apparently the drug can inhibit the spread of the organism, but an intrinsic antibody response is necessary before the infection can be overcome. The lack of immunity response may explain the recurrence of fever and symptoms of disease when the drug is discontinued. In these cases antisera are probably indicated when available.

DOSAGE AND TOXICITY

Determination of dosage was influenced by age, weight, and degree of illness of the patient. Further experience probably will demonstrate how much of the drug is necessary by age or by weight, for the best results. The concentrations in the blood have been determined by Marshall's method for sulfanilamide, using sulfapyridine as a standard. The values obtained ranged from 0.2 mg. to 9.4 mg. per cent. The number of cases treated is too small to be conclusive, but the results indicate that concentration of approximately 2 mg. per cent is sufficient.

TABLE II

PATIENTS WITH BRONCHOPNEUMONIA TREATED WITH SULFAPYRIDINE

CASE NUMBER	AGE (MO.)	DIAGNOSIS	ORGANISM	DAYS OF ILLNESS BEFORE TREATMENT	DOSAGE OF SULFAPYRIDINE IN GRAMS/DAY	DAYS OF TREATMENT	LEVEL OF SULFAPYRIDINE IN BLOOD, MG. PER CENT	TEMPERATURE RESPONSE*	W. B. C. RESPONSE*	RESULT	COMMENT
14	18	Broncho-pneumonia	B-Hemolytic streptococcus	28	1.2	11	1.1	Fell from 38.8 to 37° C. in 24 hr. (102 to 98.6° F.)	Fell from 24,500 to 11,500	Improved	Pneumonia complicated pertussis. Previous therapy of slight value. Marked improvement noted as soon as sulfapyridine was started. Small area of consolidation remained at time of discharge, but child was afebrile and gaining weight. Returned 3 weeks later with process about unresolved area. Responded rapidly to sulfapyridine therapy and remained well.
	18	Broncho-pneumonia	B-Hemolytic streptococcus	2	1.2	4	?	Fell from 39.8 to 37° C. in 24 hr. (103.8 to 98.6° F.)	Fell from 32,500 to 13,500	Well	
15	8	Broncho-pneumonia	B-Hemolytic streptococcus	2	1.8	2	?	Rose from 39.5 to 41° C. in 36 hr. (103 to 106° F.)	Rose from 7,900 to 8,900	Expired	Fulminating infection which did not respond to any type of treatment. Expired in 36 hours.
16	2	Broncho-pneumonia	Hemolytic *Staphylococcus aureus*	1	1.8	3	?	Rose from 40.5 to 42° C. in 72 hr. (105 to 107.6° F.)	Rose from 12,000 to 20,000	Expired	No response to treatment. Autopsy showed extensive pulmonary involvement with early necrosis.

*The first temperature reading and white blood cell count are those at the beginning of treatment. The last white blood count is that obtained when treatment was discontinued.

TABLE II—CONT'D

17	24	Broncho-pneumonia	†	7	1.2	2	1.6	Fell from 38.4 to 37° C. in 24 hr. (101.5 to 98.6° F.)	Fell from 28,000 to 11,000	Well	Initial improvement rapid, but recovery slow thereafter. Vomited on first 2 days of treatment.
18	18	Broncho-pneumonia	Hemolytic *Staphylo-coccus aureus*	5	1.8	4	†	Fell from 38.7 to 37° C. in 24 hr. (102 to 98.6° F.)	Fell from 15,800 to 9,900	Well	Treated with sulfanilamide 4 days without benefit. Responded immediately to sulfapyridine. Pneumonia bilateral.
19	3	Broncho-pneumonia	Hemolytic *Staphylo-coccus aureus*	3	--	--	--	Rose from 39.9 to 42° C. in 8 hr. (103.6 to 107.6° F.)	Admission count = 17,000	Expired	This patient received only one dose of the drug before exitus. Moribund on admission.
20	1	Broncho-pneumonia	Hemolytic *Staphylo-coccus aureus*	†	1.2	3	9.4	Afebrile	±14,000	Well	Probably an aspiration pneumonia. Responded slowly to therapy. Methemoglobinemia and cyanosis marked. Diarrhea developed when treatment was started. All toxic symptoms cleared when the drug was withdrawn.
21	24	Broncho-pneumonia	Hemolytic *Staphylo-coccus aureus* and *B-Hemolytic streptococcus*	6	3.0	26	1.7	Varied widely	Varied widely	Improved	Pneumonia complicating laryngeal diphtheria with tracheotomy. Sulfanilamide for 4 days without benefit. Improvement started when changed to sulfapyridine, and slow recovery took place. Resolution slow. Withdrawal of drug followed by sharp rise in temperature which subsided when chemotherapy was resumed.
22	24	Broncho-pneumonia	*Streptococcus viridans* and *Staphylo-coccus albus*	2	3.0	5	†	Fell from 40.4 to 37° C. in 24 hr. (104.8 to 98.6° F.)	Fell from 52,000 to 10,000	Well	Rapid fall in W.B.C. and temperature suggested pneumococcal etiology, but none found. Course short and uneventful.

TABLE III

PATIENTS WITH MISCELLANEOUS CONDITIONS TREATED WITH SULFAPYRIDINE

CASE NUMBER	AGE	DIAGNOSIS	ORGANISM	DAYS OF ILLNESS BEFORE TREATMENT	DOSAGE OF SULFAPYRIDINE GM./DAY	DAYS OF TREATMENT	LEVEL OF SULFAPYRIDINE IN BLOOD, MG. PER CENT	TEMPERATURE RESPONSE*	W. B. C. RESPONSE*	RESULT	COMMENT
23	6 yr.	Osteomyelitis and sepsis	Hemolytic *Staphylococcus aureus*	28	1.2	7	0.2	Fell from 38.2 to 37° C. in 24 hr. (101 to 98.6° F.)	No change	Slightly improved	Critical period treated with antitoxin, transfusions and drainage. Temperature remained between 38 and 39° C. until chemotherapy was started. Remained afebrile.
24	7 yr.	Acute osteomyelitis	Hemolytic *Staphylococcus aureus*	8	3.6	5	†	Fell from 38.5 to 37° C. in 24 hr. (101.5 to 98.6° F.)	Fell from 23,000 to 14,000	Improved	Acute phase subsided promptly. Drug supplemented surgical drainage and transfusions. Blood culture negative.
25	8 yr.	Meningitis, sepsis and brain abscesses	Hemolytic *Staphylococcus aureus*	7	5.4	20	†	Remained elevated ±41° C. (105.6° F.)	Varied 10,000 to 30,000	Expired	Patient practically moribund from time of admission. Transfusions, antitoxin and chemotherapy only served to prolong her course.
26	7 yr.	Meningitis after head injury	None recovered	10	3.0 3.6	5 6	4.6 2.5	Fell from 40 to 37° C. in six days (105 to 98.6° F.)	Fell from 24,000 to 2,400	Well	Spinal fluid on admission showed 76,000 cells. Four days later only 56. Sulfanilamide used for 4 days, but temperature remained elevated and he failed to improve. Sulfapyridine then started with noticeable improvement and gradual return of temperature to normal. W.B.C. at 2,400 showed 53 per cent granulocytes in differential. Sulf- and methemoglobin both noted.

*The first temperature reading and white blood cell count are those at the beginning of treatment. The last white blood count is that obtained when treatment was discontinued.

obtained when treatment was discontinued.

TABLE III—CONT'D

27	4 yr.	Osteomyelitis	None recovered	1	2.0	3	?	Afebrile	Admission count = 15,000	Well	Diagnosis not clear. Point tenderness over hip region subsided in 2 days and has not recurred.
28	1 wk.	Epidermolysis bullosa	Hemolytic *Staphylococcus aureus*	7	1.0	10	?	No change noted	±5,300	Expired	No effect on skin lesions. Developed secondary impetigo. Autopsy revealed lateral and longitudinal sinus thrombosis.
29	7 mo.	Cellulitis of hand and shoulder	Hemolytic *Staphylococcus aureus*	7	2.0	10	?	Fluctuated ±40° C. (104° F.)	Rose from 15,000 to 22,000	Expired	Treated by compresses, incision and drainage of abscesses, transfusions and antitoxin, as well as sulfapyridine. Course steadily downhill.
30	3 wk.	Impetigo neonatorum	Hemolytic *Staphylococcus aureus*	7	--	--	--	------	------	No change	Two per cent sulfapyridine ointment applied to several areas. These did not do as well as control areas. Drug not given by mouth.
31	6 yr.	Meningitis	*M. catarrhalis*	14	2.0	7	4.3 5.7	Fell from 39.2 to 36.8° C. in 24 hr. (103 to 98° F.)	Fell from 13,000 to 5,000	Well	Classical story of meningitis. Symptoms disappeared with rapidity and complete recovery took place in one week. Cyanosis and methemoglobin formation marked.
32	12 yr.	Ruptured appendix	None	6	2.0	10		No change	Fell from 22,000 to 6,400	Improved	Only noticeable effect of the drug in these cases was a slight increase in the normal rate of recovery. Both patients were doing fairly well when the drug was discontinued.
33	8 yr.	Ruptured appendix	None	4	2.0	10		Slight fall	Fell from 23,000 to 9,000		

Early reports indicated that the drug had approximately one-fourth the toxicity of sulfanilamide,[11] but Marshall, Bratton and Litchfield[12] report that, because of the low solubility of sulfapyridine, the blood level to be expected from a given dose cannot be predicted. Using the soluble sodium salt of the drug, they found that mice with concentrations of as low as 63 mg. per cent in the blood showed marked toxic symptoms. They recommend cautious employment of the drug. Evidently one cannot use the drug without the cautions ordinarily employed when giving sulfanilamide. Twenty-eight per cent of our patients had nausea and vomiting during treatment. This was not severe enough to warrant discontinuing the therapy. Diarrhea appeared in one case, but stopped immediately when the drug was withheld. Cyanosis was marked in three cases, but since ten of the patients were colored the actual number may have been higher. Methemoglobin was reported in several cases and sulphemoglobin in one. Hemolytic anemia has not been recorded, but in Case 10 the hemoglobin fell from 102 per cent to 64 per cent in three days. Other patients lost from 10 to 20 per cent during treatment. In no instance has the hemoglobin reached a critical level, and the fall always stopped when the drug was discontinued.

Agranulocytosis[13] has been reported once, but the patient recovered when the drug was stopped, and the etiology of the low count was not entirely certain. In our series one count of 2,400 was recorded, but there were 53 per cent granulocytes in the differential count.

Lloyd, Erskine, and Johnson[7] reported gastrointestinal upsets in 9 per cent of their patients, skin reactions in 6 per cent, headaches in 10 per cent, and one case of photosensitization of the skin.

Purpura, psychoses, peripheral and central neuritis, and drug fever have not been encountered either in the patients described in the literature or in the patients treated in our series.

DISCUSSION

Sulfapyridine, a new chemotherapeutic agent, has been used in the treatment of thirty-three children suffering from a variety of diseases. The results are presented with comments.

The most effective use of the drug in this series seems to be in pneumococcal infections. Improvement was noted within forty-eight hours. The total white blood count seems to be the best indicator of progress, since a delay in resolution and spread of the process appear to occur when the count remains high. This suggests that specific antiserum may be of value when the patient's antibody response is slow.

In bronchopneumonia the drug seems promising and has been of benefit in cases in which other treatments failed. The infections treated were caused by beta hemolytic streptococcus and hemolytic *Staphylococcus aureus.*

The ease of administration and the effectiveness of the drug represent a saving of time and a notable therapeutic advance in the treatment of pneumonias.

A miscellaneous group of conditions treated suggests that the drug may have wider applications and deserves further study.

Toxic effects such as vomiting, cyanosis, methemoglobin formation, and a fall in hemoglobin during treatment have been noted and indicate that the same caution must be employed as with the use of sulfanilamide.

The drug is effective in smaller doses and in lower concentrations than sulfanilamide.

In almost all cases the administration of the drug has been accompanied by a lowering of the temperature. This has been so constant that an antipyretic effect is suggested.

The sulfapyridine has been very generously supplied by Calco Chemical Company, Inc., and Merck & Company, Inc.

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OILS AS SUBSTITUTES FOR BUTTER FAT IN INFANT FEEDING

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EFFORTS to produce a dilution of cow's milk with a composition similar to that of human milk for purposes of infant feeding have not been very successful because a corresponding amount of fat in cow's milk is poorly tolerated by the infant. Although the cream-milk of Biedert and the "maternalized milk" of Gaertner had percentage compositions similar to that of human milk, the practical results were not satisfactory, as disturbances of nutrition, vomiting, diarrhea with fatty stools, and toxic conditions were produced.

Better results were obtained with the butter-flour food of Czerny-Kleinschmidt (1919). This food differs from human milk in that it contains starch, but the method of obtaining the butter-flour decoction makes a good emulsion of the butter easily available to every mother. There are two difficulties, however: first, the butter-flour food cannot be given during the first weeks of life, and, second, it is imperfectly utilized (according to Stolte and Noak, from 17 to 30.4 per cent of the fat ingested is eliminated with the stools).

In a series of researches in the Pediatric Clinic in Berlin (1921) under the direction of Czerny, I studied the correlation of the various alimentary ingredients which would assure the best utilization of fats in cow's milk. It was demonstrated that under identical conditions the utilization of the fat is better if the carbohydrates are represented by maltose or malt extract, while utilization is poorer if, by the addition of "plasmon," the proportion of protein is increased or if, by the addition of calcium lactate, the proportion of calcium salt is increased. In the course of such research it was observed that even with the best correlation there was less efficient utilization of fats than with human milk. The difference is not due to the degree of subdivision of the fat particles, because the subdivision into minute globules by emulsifying machines can take place without affecting the difference in utilization.

In the course of these experiments I was able to establish the fact that the fats extracted from the stools have a higher fusion point (in every case above 41° C.), while those extracted from the corresponding food have strikingly lower ones. I gathered from this, as a working hypothesis, that from the fatty mixture of the food the fats with lower melting points would be absorbed and those with higher melting points would be eliminated with the stools.

To explain the difference in the degree of utilization of fats in human milk and in cow's milk, it is necessary to consider the different physical

(melting point) and chemical characteristics (proportion of saturated and unsaturated triglicerides) of the various fat mixtures. It is known that, excluding the volatile fatty acids, cow's milk fat contains about 70 per cent of tripalmitin and 30 per cent of triolein, while the fat of human milk, according to the recent determinations of Polonowski, contains about 70 per cent of triolein and only 30 per cent of tripalmitin and tristearin. In 1923 I was able to determine by Benseman's method not only the terminal point of fusion, an average of 31.4° C. (coinciding with the preceding determinations of Ruppel and Laves), but also the point of initial fusion, which was found at a very much lower temperature, an average of 18.4° C. These preliminary observations led me to think that, if the efficient utilization of the fat of human milk were due to its greater content of triolein, improved retention of the fat of cow's milk could be obtained with an increase of the proportion of triolein. This could be accomplished practically by substituting a vegetable oil rich in triolein, as for instance olive oil, for the butter of cow's milk.

VEGETABLE OIL SUBSTITUTES

A few authors had attempted to substitute vegetable oils in the dilutions of cow's milk, but with different purposes in view. Other vegetable oils, such as coconut oil and cottonseed oil, were used in the feeding of infants by Rockwood and Swikes (1919) and by Emmett Holt, Sr., Courtney, and Fales (1919), who proved that these can be substituted for butter, in a great measure, to provide more economically the needed fats. However, they have not shown any important differences in the utilization between butter, coconut oil, or cottonseed oil.

Ladd (1915) by adding mechanically emulsified olive oil to diluted cow's milk was able to produce a good increase of weight in infants. He did not, however, follow up these clinical observations by any research on fat metabolism, and his method is not widely used because of the difficulty of obtaining a good emulsion of oil in milk.

Boschân (1921) attempted to substitute oil of poppy and other vegetable oils for the butter in the Czerny-Kleinschmidt food; he limited himself to the statement that clinically as good results can be obtained with vegetable oils as with butter in the Czerny-Kleinschmidt food. No research has been published by this author on fat metabolism.

My researches, which were reported in 1923, were founded on studies of fat metabolism as well as clinical observations. They are, as far as an examination of the literature discloses, the first which have demonstrated experimentally that the more completely olive oil is substituted for milk fat, the more complete is the absorption. In Tables I and II are given the results of twelve studies on the ingestion-retention balance of fat. If from Table I we use the figures expressing the percentage of ingested fat that is eliminated, we are able to express the essential data in Table II.

TABLE I

NUMBER OF EXPERIMENT	NAME	AGE (MONTHS)	WEIGHT (KG.)	FOOD*			INGESTED† AS FATTY ACIDS (GM.)	ELIMINATED† WITH FECES: AS FATTY ACIDS (GM.)	ELIMINATED† WITH FECES: % OF INTRODUCTION	BALANCE AS FATTY ACIDS (GM.)	ABSORPTION % OF INTRODUCTION
1	G. A.	9	8.700	Butter-flour	cow's milk	gm. 500	60.789	12.870	21.17	47.919	78.83
					water	gm. 500					
					sugar	gm. 40					
					wheat flour	gm. 40					
					butter	gm. 35					
2	G. A.			Oil-flour	cow's milk	gm. 500	56.748	5.652	9.95	51.096	90.05
					water	gm. 500					
					sugar	gm. 35					
					wheat flour	gm. 35					
					olive oil	gm. 30					
3	G. A.			Oil-flour with skim milk	skim cow's milk	gm. 500	74.740	2.058	2.75	72.682	97.25
					water	gm. 500					
					sugar	gm. 50					
					wheat flour	gm. 50					
					olive oil	gm. 50					
4	M. G.	8	5.100	Butter-flour	cow's milk	gm. 350	54.050	6.350	11.75	47.700	88.25
					water	gm. 350					
					sugar	gm. 35					
					wheat flour	gm. 35					
					butter	gm. 35					
5	M. G.			Oil-flour	cow's milk	gm. 350	67.725	5.657	8.35	62.068	91.65
					water	gm. 350					
					sugar	gm. 35					
					wheat flour	gm. 35					
					olive oil	gm. 35					

*In 24 hours.
†In 48 hours' duration of the experiment.

TABLE I—CONT'D

6	R. R.	12	8.100	Butter-flour	cow's milk gm. 500 water gm. 500 sugar gm. 45 wheat flour gm. 40 butter gm. 35	61.218	4.503	7.36	56.715	92.64
7	R. R.			Oil-flour	cow's milk gm. 500 water gm. 500 wheat flour gm. 40 sugar gm. 45 olive oil gm. 40	82.620	5.605	6.78	77.015	93.22
8	R. R.			Oil-flour with skim milk	skim cow's milk gm. 500 water gm. 500 sugar gm. 50 wheat flour gm. 50 olive oil gm. 50	76.627	4.089	5.34	72.538	94.66
9	L. D.	8	8.100	Butter-flour	cow's milk gm. 500 water gm. 500 sugar gm. 30 wheat flour gm. 30 butter gm. 30	71.820	12.771	17.78	59.049	82.22
10	L. D.			Oil-flour	cow's milk gm. 500 water gm. 500 sugar gm. 30 wheat flour gm. 30 olive oil gm. 30	77.548	6.598	8.51	70.950	91.49
11	B. S.	11	7.800	Oil-flour	cow's milk gm. 500 water gm. 500 sugar gm. 45 wheat flour gm. 40 olive oil gm. 35	91.014	7.027	7.72	83.987	92.28
12	B. S.			Oil-flour with skim milk	skim cow's milk gm. 500 water gm. 500 sugar gm. 45 wheat flour gm. 40 olive oil gm. 40	91.378	2.880	3.15	88.498	96.85

Thus since 1923 the importance of the chemical composition of the fat mixtures contained in food has been established, and particularly has it been demonstrated that the fatty substances contained in olive oil were better utilized than those contained in cow's milk. There was still the question whether the better retention of olive oil was due to the low melting point, to its iodine index, or to the chemical characteristics of the molecule of triolein which constitutes over 90 per cent of olive oil. But for practical purposes the fact that olive oil was better utilized than butter fat was made evident in a way that could not but be later confirmed by Italian and foreign researchers.

TABLE II

PERCENTAGE OF INGESTED FAT ELIMINATED

PATIENT	BUTTER-FLOUR FOOD (%)	OIL-FLOUR FOOD (%)	OIL-FLOUR FOOD WITH SKIM MILK (%)
R. R.	7.36	6.72	5.34
M. G.	11.75	8.35	–
G. A.	21.17	9.95	2.75
L. D.	17.78	8.51	–
B. S.	–	7.72	3.15
Average	14.51	8.25	3.74

Gironcoli was able to prove in the Institute for Infants at Trieste that my oil-flour food was better tolerated by infants from the second month on than a corresponding food in which butter had been substituted for oil. In ten cases in which the fat metabolism was studied, the oil-flour food gave an average absorption of 91.96 per cent. Moggi, Mura, and Battistini later confirmed these studies both clinically and by determinations of fat metabolism.

L. Emmett Holt, Jr., and his collaborators (1933 and 1935), in a very extensive study, contributed also to the answer of the question which interests us. In four experiments on fat metabolism carried out with an olive oil food, the retention varied from 92.1 to 96.7 per cent, that is, with figures which agree with mine. He made his observations on groups, and hence the comparisons which he draws on the various averages are not always sufficiently demonstrative, as it is well known that the fat utilization and tolerance in general vary according to the individual constitution of the child.

On the other hand, Holt extended his investigations over a large number of vegetable, animal, and chemically pure fats, adding the following important proofs for our argument: There exists a definite relation between the length of the carbon chain and the degree of saturation of fat and the degree of utilization. The absorption of a fatty mixture would be aided by the presence of fats containing one or more double links and likewise by fats with relatively short carbon chains. On the other hand, absorption would be hindered by the presence of saturated fats and fats with long carbon chains. If the fatty substances with long

carbon chains are arranged according to the progressive degree of the iodine index, the absorption is proportional to the iodine index. On this basis the absorption of a fatty mixture could be calculated approximately, provided the percentage of the various fats, saturated or unsaturated, contained in it is known.

More recently (1937) Blatt and Harris, using the American dry milk, olac, in which oil is substituted for the fat of cow's milk, have again confirmed the good results (increase in weight and stature) that an oil-food can give in the mixed or in the artificial feeding of infants.* Their research on fat metabolism, limited to four children, two of whom were fed with evaporated milk and two with olac, compares the averages obtained in the two groups. They believe that they can conclude in favor of better absorption of fat when olac is fed, although the same individual with equal feeding in different periods had given differences of from 75.63 per cent to 83.75 per cent with evaporated milk and from 80.88 per cent to 95.67 per cent with olac. Here, also, as in Holt's researches, is the difficulty of comparing the absorption of fats in different individuals, because of the individual and constitutional difference of tolerance and utilization of fats.

Recently some Italian physiologists, Peretti in the Institute of Artom, and Roncato, confirmed the finding of a very good absorption of olive oil in experimental animals (rats) and in the adult human being. In our clinic in Padua, Radici and Pieriboni, during successive experimental periods, other things being equal, have been able to compare in the same children the utilization of butter, various vegetable oils and a series of chemically pure fatty substances.

Substituting one vegetable oil for another in infant feeding makes a difference (Table III). In sixteen trials olive oil has given an average absorption of 93.30 per cent. Other oils with their relative values of absorption follow: soybean oil, 91.2 per cent (six trials); oil of poppy, 90.8 per cent (two trials); linseed oil, 82.89 per cent (three trials); sesame oil, 74.61 per cent (two trials); coconut oil, 72.39 per cent (two trials).

Also two dry oil-milks in which a vegetable oil is substituted for the fat of the milk (olac and the oil-milk product prepared according to my formula by Nestlé) were tried. They gave different values of absorption in the same infants—the Nestlé product, 94.05 per cent (two trials), and olac, 77.8 per cent (two trials). The difference may be due to the fact that in the preparation of the first product pure Tuscan olive oil is used while we are not quite sure that only olive oil is used in the preparation of olac.

*These authors state that Holt was the first to demonstrate that an oil rich in triolein was better absorbed than butter. They state that "the knowledge that fats, other than those in milk, were more completely absorbed, presented a new phase in infant feeding." If we want to adopt such an expression, this new phase was initiated in Italy in 1923. But triolein is an important constitutent (70 per cent) of the fatty mixture in human milk.

TABLE III

PERCENTAGES AND AVERAGES OF ABSORPTION OF VARIOUS FATS

FATS	OLIVE OIL (%)	SOYBEAN OIL (%)	POPPY OIL (%)	LINSEED OIL (%)	SESAME OIL (%)	COCONUT OIL	BUTTER (%)	PURE FATS			DRY OIL-MILKS	
								TRIOLEIN (%)	TRIELAIDIN (%)	TRIPALMITIN + TRISTEARIN (%)	NESTLÉ (%)	OLAC (%)
Case 1	90.61 94.55 96.10 95.08	93.80	91.7	87.4	76.9	79.69	50.17	98.6 96.5	60.5	58.5		
Case 2	88.62 92.53	95.4	90									
Case 3	93.8 91.6	88.32		76.28	72.32							
Case 4	95.5 96.2	90.4										
Case 5	94.6 97.8	91.6										
Case 6	93.02 95.20											
Case 7	90.33 92.70	91.29		85.00		65.1		98.3	34.3	53.3	93.2	73.4
Case 8							49.95	97.75	62.9	31.8	94.9	82.2
Average percentage of absorption	93.39	91.2	90.85	82.89	74.61	72.39	50.06	97.77	49.2	47.83	94.05	77.8

If we now consider the utilization of chemically pure substances, we find that a mixture of two parts of tripalmitin and one part of tristearin has given an average utilization of 47.85 per cent (three trials). Pure triolein, used instead, averaged 97.77 per cent (four trials), which is the highest percentage reached in our studies.

Trielaidin, an isomer of triolein, with a much higher melting point (triolein 4° C., trielaidin 37° C.) has given, all other things being equal, an average utilization of 47.83 per cent (three trials) in the same children. Thus two isomer unsaturated triglicerides which have a double linkage in the same position have shown markedly different values of utilization. These have been much higher for the isomer with the lower melting point, while the iodine index for both is naturally the same.

If we compare the results obtained from the different oils with their physical and chemical characteristics, we find no evident relation between iodine index, index of saponification, and the percentage of utilization (Tables IV and V). On the other hand, there seems to exist a relation between the chemical composition of the various oils and their percentage of utilization. The values of absorption have been higher for the vegetable oils which contain a greater percentage of triolein. To a less degree this is to be said of those oils which contain a greater quantity of linolein, another unsaturated triglicerides, with two double linkages. Cow's milk fat, which is rich in saturated triglicerides, as has been observed with a mixture of tripalmitin and tristearin, is utilized poorly.

TABLE IV

PHYSICAL CONSTANTS AND CHEMICAL COMPOSITION OF SOME FATTY SUBSTANCES USED IN THE EXPERIMENTS

Fats	OLIVE	SOYBEAN	LINSEED	POPPY	SESAME	COCONUT	BUTTER
Iodine index	80 - 84	121-138	170-190	134-143	103-112	86 - 94	26 - 39
Index of saponification	187-193	192-194	188-195	190-198	188-195	246-258	209-240
Melting point	19°-27°	20°-28°	18°-21°	20°-30°	24°-30°	24°-27°	38°-45°
Oleic acid	93%	60%	5%	30%	72%	2%	23.3%
Linoleic acid	6%	25%	80%	65%	15%		
Linolenic acid		5%	15%	5%			
Palmitic acid						2%	27.5%
Stearic acid						5%	12.6%
Miristic acid						20%	20.1%
Tauric acid						45%	
Butyric acid							11.7%
Caproic acid							2.3%
Caprylic acid							1.9%

TABLE V

TRIOLEIN	TRIELAIDIN	TRIPALMITIN 2 P.	TRISTEARIN 1 P.
Melting point 4° C.	37° C.	71° C.	65° C.
Iodine index 89.9	89.9	2.4	

CLINICAL EXPERIENCE

Having verified in a sufficient number of experiments the efficient assimilation of the oil-flour food for brief periods of trial, we have been interested from the beginning of our study in the way in which an oil-food would be tolerated by infants over a long period of time. As our first researches go back to 1922, we have had sufficient time to make many observations on the indications and contraindications, the advantages that can be obtained, and the caution necessary in the use of this type of food. Our clinical experience has been supplemented by the necessary laboratory study and frequent determinations of the fat balance.

We have been able to demonstrate that oil-flour feeding with olive oil is not only well utilized for limited periods of time but that it is also well tolerated when used continuously for months and even for the whole period of nursing.

Charts 1, 2, and 3 of poorly nourished infants who for months on a diet of the usual dilutions of cow's milk presented a weight curve oscillating around a horizontal line or declining, show marked and continuous increases from the start of the oil-flour feeding.

We have studied the absorption of various fats in pathologic conditions in which the utilization of the fats of cow's milk is usually very poor, as in celiac disease. In Table VI are shown the values obtained by Frontali and Radici in a child, 7 years of age, who presented every sign of Herter's digestive insufficiency. In this case, as in normal infants, it cannot be said that the utilization parallels the iodine index of the various fats. Olive oil, oil of poppy, and pure triolein were utilized best. Thus in this case the comparison between triolein and trielaidin revealed, as in normal infants, a far greater utilization of triolein (94 per cent) than of trielaidin (63.31 per cent).

The periods of olive oil feeding were characterized by a weight increase, which reached 2,300 gm. in 78 days, that is, 29.4 gm. a day, while a corresponding feeding with butter, with an equal number of calories,

TABLE VI

FOOD WITH	IODINE INDEX	INGESTION (GM.)	ELIMINATION WITH THE FECES (GM.)	BALANCE (GM.)	UTILIZATION (%)
Butter	30.7	12.40	5.30	7.10	57.25
Butter	30.7	11.50	5.20	6.30	54.78
Sesame oil	103.0	11.70	4.24	6.46	55.21
Coconut oil	13.7	14.20	4.79	9.41	66.26
Olive oil	83.4	15.78	1.92	13.86	87.83
Olive oil	83.4	11.90	1.48	10.42	87.56
Olive oil	83.4	14.19	1.27	12.92	91.05
Olive oil	83.4	13.62	0.98	12.66	92.95
Oil of poppy	128.4	10.44	0.69	9.75	93.39
Triolein	89.9	12.00	0.62	11.37	94.75
Trielaidin	89.9	12.51	4.59	7.92	63.31
Tripalmitin 2 p. Tristearin 1 p.	2.4	8.02	2.89	5.13	63.96

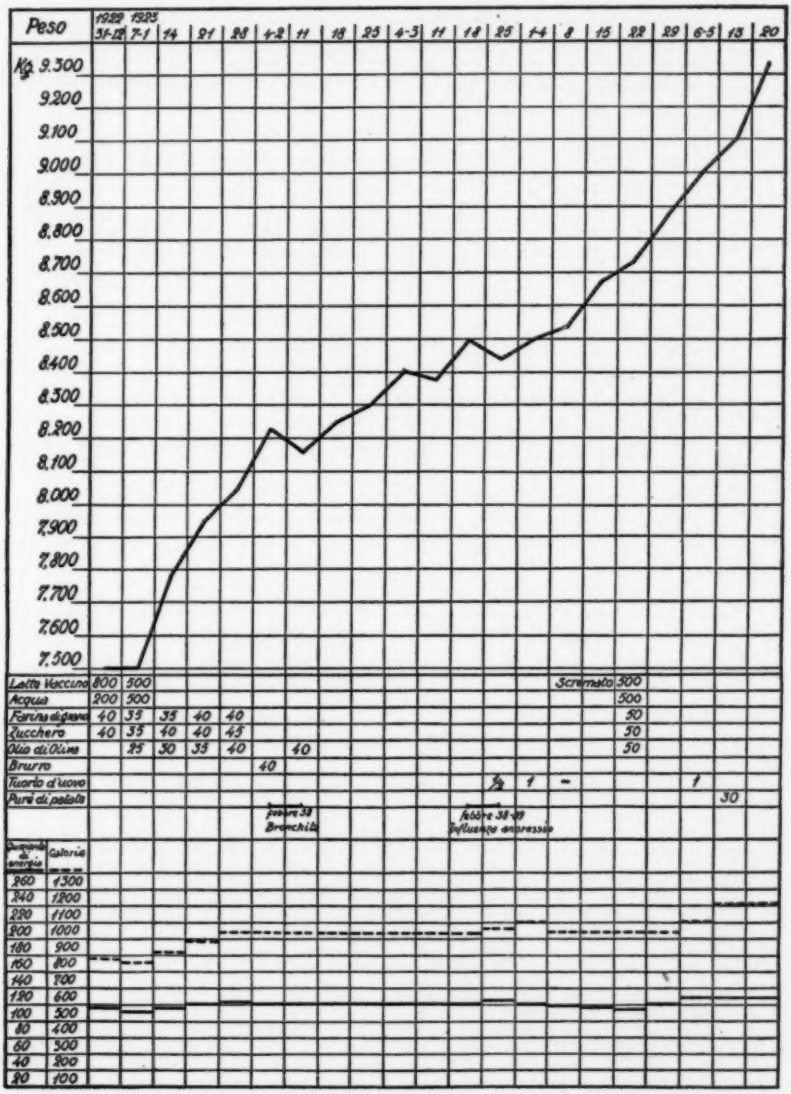

Chart 1.—R. R., aged 8 months, on artificial feeding, entered the clinic with severe gastroenteritis, weighing 6.770 kg. Recovery after appropriate treatment. Subsequent dyspepsia with fat intolerance. After three months the child still weighed 6.750 kg. With skim milk feeding diluted 2 to 3, with the addition of wheat meal, the infant gained in weight to 7.500 kg. For two weeks the weight fluctuated without increasing, although the feces were normal. At this point the oil-flour food was begun.

The chart shows a rapid and regular growth, interrupted only by parenteral infections which were followed by quick recovery and renewed growth. The baby could tolerate without inconvenience large quantities of olive oil, up to 50 grams a day, with normally formed stools, while before he had shown a persistent intolerance to cow's milk fat. The same intolerance was again observed when, for experimental purposes, olive oil was replaced by the same quantity of butter. Fatty stools were again noted and the weight dropped. Substituting olive oil for butter gave again a regularly increasing weight curve. (Results of fat metabolism studies of this child are to be found in Table I, experiments 6, 7, and 8.) (Charts 1, 2, and 3 from Frontali, "Studi sui grassi," Florence, 1924, Niccolai.)

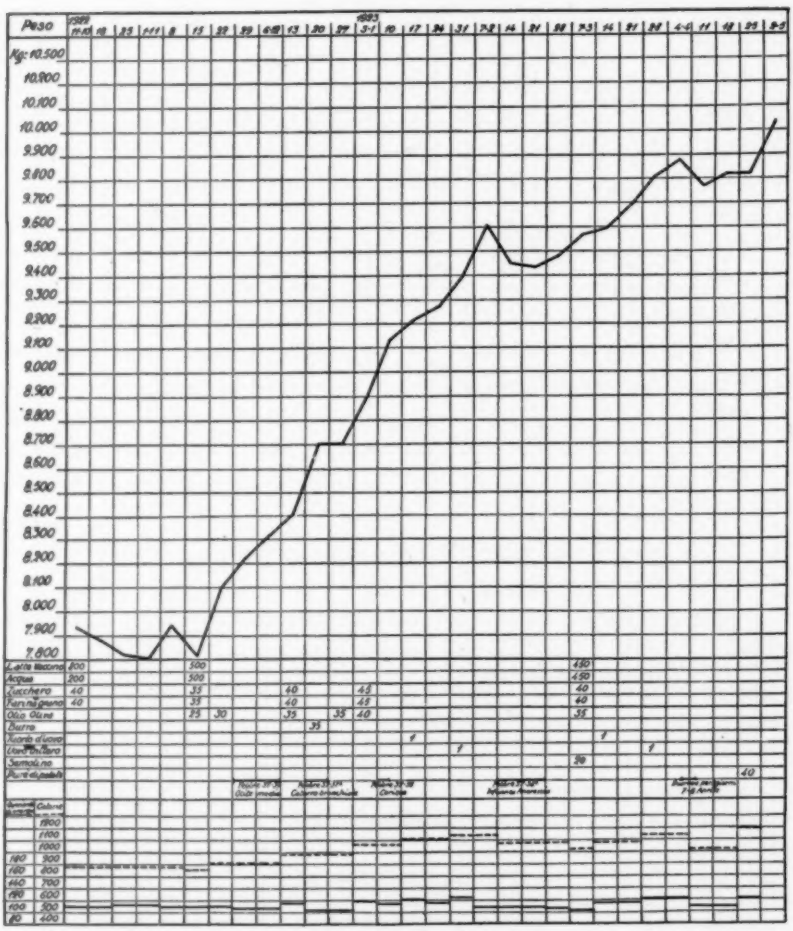

Chart 2.—G. A., born of a tuberculous mother, entered the clinic at the age of 40 days, having been breast-fed up to that time. Weight at time of entrance was 4.180 kg. Von Pirquet test was negative. Since the artificial feeding with diluted cow's milk and 2 per cent rice or wheat meal was begun, the infant grew irregularly; the weight curve fluctuated. The feces were repeatedly curdy, and regurgitations were frequent. At 8 months the weight was 7.810 kg. It varied up and down for a month, but the infant did not grow in spite of the high caloric value of the food. Under these circumstances the oil-flour food was started in the quantities indicated in the chart.

Although the caloric value of the food was initially the same as that given before, rapid and regular growth followed. Growth was stopped or reduced only by parenteral infections. During a week, for experimental purposes, butter was substituted for the oil, and growth was correspondingly stopped during this time.

The child left the clinic in normal condition: weight 10 kg.; anterior fontanel reduced; eight teeth; no sign of rickets. (Results of fat metabolism studies of this child are given in Table I, experiments 1, 2, and 3.)

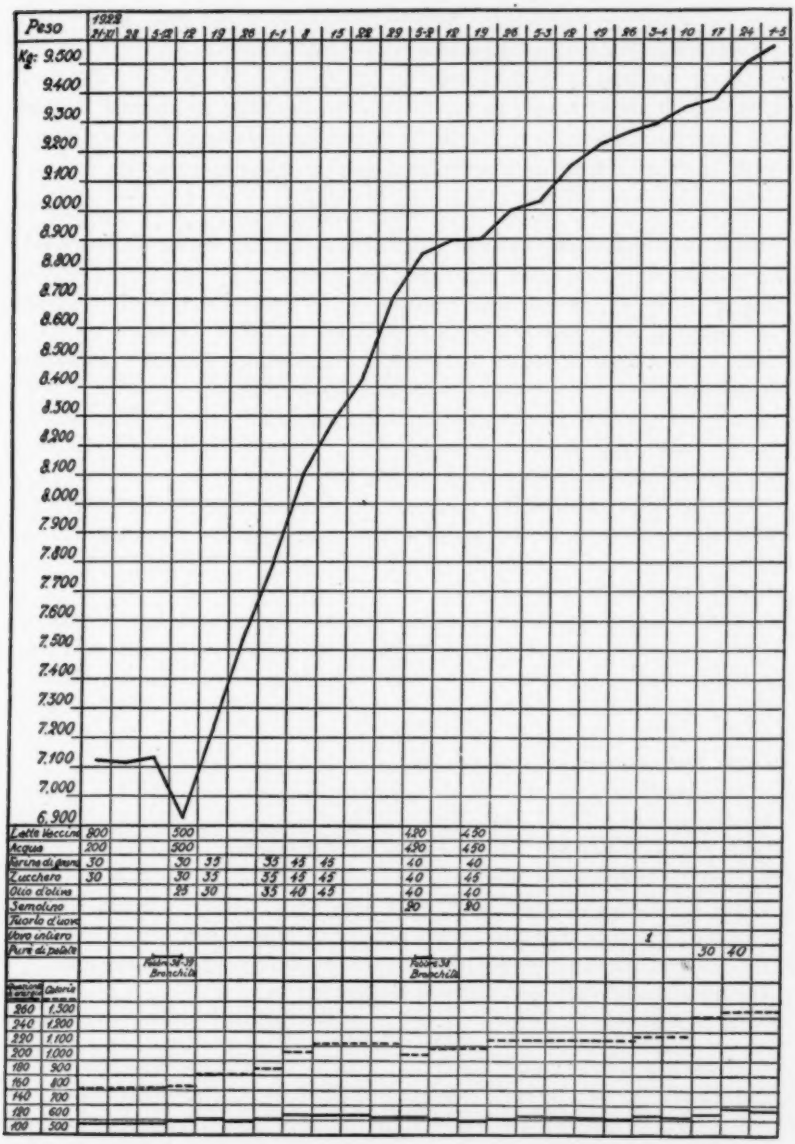

Chart 3.—Z. L., born of a tuberculous mother, was an artificially fed, dystrophic infant, weighing 6.900 kg. at 16 months of age. The anterior fontanel was wide open, only two teeth had erupted, and rickets of the skull and thorax was present.

The graph shows a loss of weight from 7.120 kg. to 6.930 kg. during the three weeks before the institution of the oil-flour food. After being fed the oil food for two months, the child gained 2 kg., that is, 33 gm. a day. After this first period bronchitis with fever (38°C.), which lasted a few days, retarded the progress. Subsequently the increase in weight continued regularly to 2.600 kg. in 84 days, that is, 30 gm. a day. After this time the fontanel was closed; the child had 16 teeth and no signs of florid rickets.

had not shown any increase. With both diets an equal amount of yeast extract (Este) was administered to the child.

In the feeding of such patients it is necessary to take into account that even if the diet poor in fats lessens the digestive symptoms, it does not lead to an increase in weight, while those diets which are supplied with fats that can be well assimilated, such as olive oil, increase weight.

OIL-MILK AND VITAMINS

The questions relative to the utilization of a fatty substance must not be confounded with those regarding the contents of vitamins A and D. The question of the vitamin contents can be settled separately. From the beginning of these studies I had in mind that the content of vitamin A in a food in which butter was replaced by olive oil might be insufficient and might lead to deficiency manifestations. In 1924 I was able to demonstrate in experiments on rats that pure olive oil is not completely lacking in vitamin A, as has later been confirmed by Viale, but soybean oil acts as though it contained none.

On the other hand, in the preparation of the food, sufficient quantities of butter can remain after the centrifugation of the milk, or, better still, the vitamins A and D can be added in measured quantities to the oil-flour food or to the dry oil-milk.

From clinical experience over many years, it was possible to demonstrate in many cases that the oil-flour food, over long periods of time, not only does not lead to A-deficiency disturbances but, on the contrary, assures an excellent and regular increase in weight and stature, superior to that which is obtained under similar conditions with the butter-flour food. These observations were confirmed by Gironcoli.

In experiments on rats, as also in experiments on infants, I was able to demonstrate (1924) that diets rich in fats, whether animal or vegetable, with deficiency of the vitamin B complex, are often accompanied by a cutaneous seborrheic condition. This can be prevented or cured by means of the addition of yeast or extract of bran. These observations were confirmed and documented histologically by Careddu. Oil feeding for a prolonged time therefore should be complemented by the addition of sufficient vitamin B complex.

CONCLUSION

From our studies and those of our collaborators, both clinical and experimental, in both normal infants and in those who have a diminished tolerance for fats, we are led to conclude that the oil-flour food or dry oil-milk in which olive oil is substituted for butter, permits an efficient utilization of fats (96.26 per cent), which approaches that of pure triolein (97.77 per cent), is well tolerated, and leads to a regular and continuous increase in weight; while a similar food in which butter is used instead of olive oil, other circumstances being equal, gives inferior results.

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A MIDSUMMER RESPIRATORY INFECTION IN AN ASEPTICALLY CONDUCTED ADOPTION NURSERY

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THE Dick[1] individual, aseptic nursery and diet kitchen technic has been in use at the Cradle since July 15, 1928. In the ten years that have elapsed, a total of 2,669 infants, mostly in the neonatal period, born in private homes and obstetric hospitals in the Chicago area, received nursery care for an average period of forty days. Although 42 infants were admitted with diarrhea, 48 with impetigo, and 8 with gonorrheal vaginitis, no instance of cross-infection of these hand-borne (contact) diseases has been observed.

In the six years, prior to the adoption of this aseptic technic, there were 942 admissions with 55 deaths (53 due to enteritis—40 contracted after admission) a case mortality rate of 6 per cent.[2]

Table I

Summary of Admissions and Deaths

	Admissions	Total Deaths	Enteritis	Respiratory	Other Causes
Before aseptic technic (1922-28)	942	55	53	2	0
Aseptic technic (1928-)	2669	22	5	9	8
Totals (1922-)	3611	77	58	11	8

Four per cent of the deaths during the first six years and 40 per cent of the deaths in the last ten years were due to respiratory disease. Nine of the twenty-two deaths during the latter period were caused by bronchopneumonia. Several infants contracted the fatal infection after admission. The infecting agent appears to have been transmitted through the air from a sick to a well infant. Numerous instances of respiratory cross-infections ("colds") were observed since 1928, despite a flawless precautionary technic (¾ height cubicles, individual, aseptic nursing care, masks, autoclaved feedings). This brief report concerns the transmission of a midsummer epidemic of respiratory disease to nine of the eleven infants in Unit 1.

On July 21, 1938, Rita, aged 15 weeks, weight, 5,440 gm. (12½ pounds), entered a cubicled crib. The ten other infants, the nurses, and the physicians were apparently well. A few hours after admission, a marked coryza and audible wheezing in the chest were noted. Within a day, the rectal temperature rose to 38.1° C. (100.5° F.). Fine râles were heard over the entire chest; a spasmodic hacking cough was present. At the end of six days the infant's general condition was quite normal, although a weight loss of 90 gm. had occurred.

Four days after Rita's admission, Marie, aged 8 weeks, weight, 3,175 gm. (7 pounds), who had spent forty-four uneventful days in a cubicled crib in the same room, developed coryza, sneezing, and bronchitis—symptoms like those observed in Rita; her highest temperature was 38.3° C. (101° F.); recovery was complete within a week. There was a weight increase of 100 gm. during the period of illness.

Five, six and seven days after Rita's admission, Curtis in the same room, Lindley, George, and Chauncey in the adjoining room, all in cubicled cribs, developed respiratory symptoms like those observed in Rita; each infant recovered within a week.

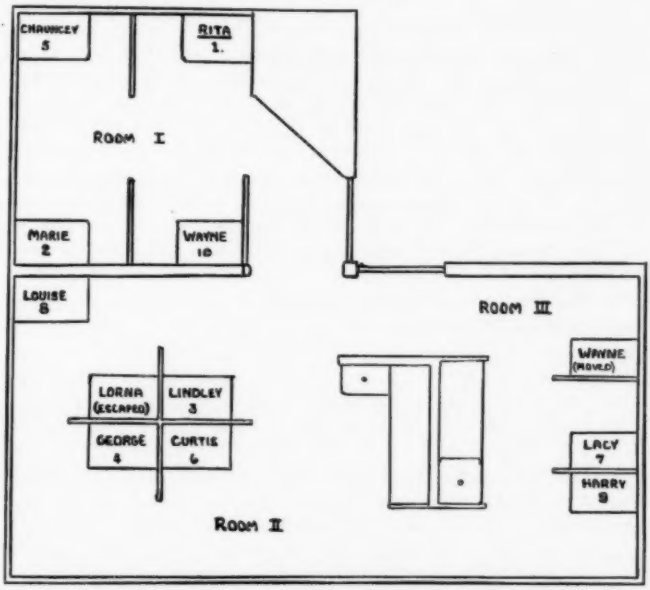

Fig. 1.—Diagram of nursing unit 1, showing position of cubicles with infants numbered in the order in which symptoms of bronchitis appeared.

Eight days after Rita's admission, Lacy, aged 7 weeks, weight, 1,815 gm. (4 pounds), a prematurely born infant, in a cubicled, incubator crib, in an adjoining room of the unit, developed symptoms of the upper respiratory infection which continued for five days; the highest rectal temperature was 38.9° C. (102° F.); recovery was uneventful.

Twelve and thirteen days after Rita was admitted, Harry, in the crib adjoining Lacy's crib, and Louise, in the second room of the unit, developed coryza, fever, bronchitis, and a hacking cough; both recovered within a week.

On July 27, 1938, Wayne, aged 10 days, weight, 3,325 gm. (7¼ pounds), was admitted into the crib adjoining Rita's, the only available cubicled crib of the unit. He was apparently well and gained 90 gm. in a

week. At that time, Marie, in the other adjoining crib, was showing early symptoms of bronchitis. Eight days after admission Wayne developed respiratory symptoms like those described. Within forty-eight hours a small area of consolidation was noted in the upper lobe of the right lung. The bronchopneumonic process spread rapidly throughout the right lung; the temperature rose to 41.1° C. (106° F.). He expired on Aug. 13, 1938, at the age of one month, ten days after the onset of symptoms.

Dr. Eustace L. Benjamin, pathologist to the Evanston Hospital, performed the post-mortem examination. He recorded the following essential pathologic findings:

The male infant was well developed and well nourished. The body length was 47 cm. The body weight was 3,920 gm. A copious, thick, brown-yellow fluid escaped from the left nostril. The subcutaneous fat tissue in the anterior abdominal wall was 4 mm. thick. The lateral position of the right pleural cavity presented an empyema cavity containing 15 c.c. of thick yellow pus. A thick fibrinopurulent pleuritis was present. There was no demonstrable fistula. Sectioned surfaces of both lungs showed edema, hyperemia, suppurative bronchitis, and miliary abscesses. The latter were associated with a perifocal acute exudative pneumonic process. Colonies of blue-staining bacteria were seen in the bronchi and abscesses (hematoxylin and eosin stain).

The myocardium and liver showed fatty changes and parenchymatous degeneration. There was an acute inflammatory reaction of the spleen. The kidneys were edematous.

Bacteriology:

Staphylococcus pyogenes aureus was isolated from the lung, empyema pus, and left nostril. No Klebs-Loeffler bacilli were found. The heart's blood culture was negative.

Lorna, the only other infant in the unit (aged 9½ weeks on the day Rita was admitted), had 51 uneventful days at the Cradle; she was dismissed sixteen days after Rita's admission, without any sign of upper respiratory infection (immune?).

Four, seven, ten, twelve, fourteen, and sixteen days, respectively, after Rita's admission, a student nurse (J. C.); the resident physician (J. M.); a (masked) visiting physician, who was near Rita during the examination by the attending physician; a graduate nurse (E. R.); a graduate nurse (B. S.); and the nursery supervisor (F. H.) developed upper respiratory infections which persisted for four to six days, with a maximum temperature of 37.2° to 37.4° C. (99° to 99.4° F.).

CONCLUSIONS

Hand-borne (contact) cross-infections (enteritis, impetigo, gonorrhea) have been prevented over a period of ten years by the Dick aseptic nursery and diet kitchen technic. Air-borne (respiratory) cross-infections have spread from sick to well infants, in spite of the Dick technic and the customary ¾ height cubicles.

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THE TREATMENT OF INFECTIONAL ASTHMA IN CHILDREN WITH FILTRATES OF CULTURES OF UPPER RESPIRATORY PATHOGENIC BACTERIA

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THE treatment of asthma may be as simple as the treatment of hay fever, but the inciting agents in asthma, if they can be determined assuredly, are often more numerous, sometimes including air-borne excitants, ingested foods, and bacterial infection in the same patient. The etiology may be further complicated by climatic, emotional, and endocrinal factors which not only aggravate but even cause a continuance of the symptoms after the primary excitants have been discovered and appropriate and presumably adequate specific therapy has been instituted. Because this etiologic background is so complex, the evaluation of the results of bacterial therapy is difficult, necessitating the study of a group of patients in whom all dominant factors except bacterial infection have been carefully excluded. A group of children has best satisfied these conditions for studying the effects of immunization with filtrates of bacterial cultures. Inasmuch as this mode of therapy is a radical departure from usual methods of bacterial treatment, the selection of the patients treated, their symptoms, the rationale of the therapy, and the results of treatment have been carefully although briefly described.

SYMPTOMATOLOGY AND SELECTION OF PATIENTS WITH INFECTIONAL ASTHMA

In the period including the years 1930 and 1936, treatment with filtrates of bacterial cultures was begun in seventy-eight children with histories and negative intracutaneous tests suggesting uncomplicated infectional asthma. Asthma occurred first in these patients following pertussis, pneumonia, a severe upper respiratory infection, or a series of colds of increasing severity. In the majority asthma occurred subsequently only during the winter after colds and respiratory infections, but some had such frequent colds that the attacks resulted in almost continuous asthma. Although a history of asthma occurring chiefly in the winter is the usual history in infectional asthma, a few of these patients have had attacks following colds during the summer, and some believed to have purely infectional asthma have had frequent attacks all summer long. Intracutaneous tests with the common air-

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borne allergens and the important foods were all negative. After treatment was started three of these children died, one following pneumonia, one after an accident, and one from peritonitis, and twelve changed their residence or stopped treatment before they had been adequately treated. Ten had food or pollen sensitivities which were overlooked when treatment was begun or else developed during the course of treatment; these patients have not been included in the group of infectional asthma because of their multiple sensitivities. The remaining fifty-three children have been treated adequately and satisfactory observation has been maintained up to the present time. To all appearances these fifty-three children have had uncomplicated infectional asthma.

When treatment was begun the ages of the children in this group ranged from 1 to 11 years. Of the fifty-three, thirty-eight were between the ages of 4 and 8 years. Immediate or distant blood relatives of forty-six had asthma or hay fever, although this history was sometimes disclosed only after careful and repeated questioning of various members of the families. All except three, who were 2 years of age or less, had had recurrent attacks of asthma following colds throughout at least one winter and many (twenty-one) had been treated unsatisfactorily one or two years before treatment with filtrates was started. Tonsillectomy had already been done on eight patients because they had frequent sore throats and colds before the onset of asthma, and twelve had their tonsils removed after the onset without affecting the course of the disease. Roentgen ray and clinical examinations have shown low grade ethmoiditis which has been treated palliatively in twenty-three of the children, and four of the older patients have had antral infections at some time necessitating irrigation. Shortly after these patients were first seen, on the strength of their histories which suggested infectional asthma and because the tests to the common allergens were negative, cultures were made and treatment with filtrates was begun. Subsequently, early in the course of treatment if a patient did not show improvement, further intracutaneous tests were made, and the effect of changing environment and diet was studied. Inoculations have been repeated each winter with filtrates made in the fall from cultures of the nose and throat and occasionally from the bronchial sputum. Most of the children have been free of symptoms or the attacks have been mild during the second year of treatment, but treatment has been continued for three years in fifteen who were not completely relieved during the second year of inoculations. Twelve have just completed their second or third year, have been free of symptoms during this year of treatment, and will not be treated further unless the asthma recurs. Thirty-two have

been symptom-free from one to four years without treatment, and six have been well for more than four years. Three of these patients have not been benefited.

SELECTION OF BACTERIAL SPECIES USED IN TREATMENT

Bacterial therapy in asthma would be facilitated if cutaneous tests with bacterial extracts could be used specifically to determine the bacteria causing the attacks. As it is, although these tests may be positive, their behavior is unlike that of other specific tests used to determine the causes of asthma and hay fever. Both immediate urticarial and delayed tuberculin-like reactions occur on testing with the proteins of the upper respiratory pathogenic bacteria.[1-3] Immediate reactions with these proteins occur almost exclusively in patients who have hay fever or asthma,[1] but the reactions vary greatly in intensity within short periods of time, often appearing and disappearing within a few weeks.[2] Usually these positive reactions cannot be passively transferred with the patient's serum. In these respects the immediate bacterial reactions differ from the urticarial reactions obtained with pollens and other protein extracts in sensitive patients, in whom the reactions are persistent and of almost uniform intensity over long periods. The delayed bacterial reactions are not peculiar to allergic (atopic) patients and, as far as can be ascertained, occur just as frequently in all patients after respiratory infections as in those with asthma. In fact, there is no evidence indicating that bacterial sensitization or a mechanism resembling that observed in specific protein sensitizations ordinarily occurs in infectional asthma; hence it is not surprising that some allergists depend on cultures alone to determine the bacterial etiology, that others attempt to correlate the cultures and cutaneous tests and some, disregarding both cultures and tests, use a mixed bacterial stock vaccine for treatment.[3]

The filtrates with which these children were treated were prepared with bacteria selected by a method combining to some extent all three methods mentioned in closing the preceding paragraph. Preliminary studies of nasal, throat, and sputum cultures made during successive attacks of asthma in a number of patients showed that except in patients with foci of infection which might harbor certain bacteria in the intervals between attacks, the bacterial flora in successive attacks of asthma was extremely variable (Table I). In these successive attacks, aside from *Staphylococcus albus* and *Streptococcus viridans* (bacteria normally resident in the nasopharynx), the flora might change completely; furthermore intracutaneous tests with the nucleoproteins of the bacteria commonly found during respiratory infections showed that the sensitivity of the patients[2, 3] in different attacks was as variable as the nasal, throat, and sputum cultures. In treating the first

few patients, bacterial tests were done frequently, but no definite correlation was observed between the cultures and the reactions to the bacterial proteins. These tests were continued as a matter of interest only and were not used to select the bacteria for subsequent treatment because it was evident that cultures and cutaneous tests made during an attack of asthma were seldom of value in determining the flora and bacterial sensitivities in subsequent attacks.[2] However, these reactions and cultures were invaluable in that they showed the extreme variability in the flora and the sensitivities to bacteria and suggested that all the common upper respiratory pathogens should be represented in the filtrates if these filtrates were to be effective as a preventive measure.[3] The ultimate method for the bacteria for the filtrates adequately satisfied most of the theoretical requirements. The nose, throat, foci of infection, and occasionally the sputum were cultured during an attack of asthma following a cold; individual filtrates were made with all the recognized pathogenic bacteria found in the cultures, then stock filtrates of other common pathogens ordinarily causing infection of the respiratory tract were added; the final mixture contained equal parts of either autogenous or stock filtrates of *Staphylococcus aureus, Micrococcus catarrhalis, Streptococcus viridans,* hemolytic streptococcus, *Bacillus influenzae,* pneumococcus (autogenous or Group I), and of pneumobacillus if this bacillus was found in the cultures. All these bacteria may be commonly found in the respiratory tract during attacks of asthma.

TABLE I

VARIATIONS IN UPPER RESPIRATORY FLORA IN SUCCESSIVE ATTACKS OF ASTHMA

PATIENT	DATE	STAPH. AUREUS	STAPH. ALBUS	STR. VIRIDANS	STR. HAEMOLYTICUS	STR. INDIF.	M. CATARRHALIS	B. INFLUENZAE
E. D.	11/13/31		+	+		+	+	
	2/ 1/32		+	+		+	+	+
	3/28/32		+		+			+
	5/12/32	+	+	+		+		
	11/ 8/32		+	+		+	+	
	2/14/33	+	+	+	+		+	+
B. A.	2/19/30	+	+		+			
	7/ 1/30		+	+		+	+	
	12/12/30			+				
	2/10/31		+			+	+	+
E. G.	10/ 8/29	+	+	+			+	
	7/ 1/30			+	+	+	+	+
	4/ 8/30		+	+			+	+
	12/ 3/30			+	+	+		+
	6/ 2/30	+	+	+		+	+	
	1/10/31		+		+	+		

RATIONALE OF FILTRATE THERAPY AND THE PREPARATION OF THE FILTRATES

Before patients with asthma were treated with filtrates, filtrates from cultures of *Staphylococcus aureus* and *Streptococcus hemolyticus* either singly or combined were being used successfully in treating chronic infectional edema.[4] This disease is caused by streptococcal or staphylococcal infection with accompanying sensitization of the infected tissues to the bacterial growth and decomposition products of these bacteria. The specificity of these infections and of the accompanying hypersensitization to bacterial products is evidenced by cultures from the diseased tissues and adjacent foci of infection, by positive intracutaneous tests with the toxins and toxin-free filtrates from cultures of these bacteria, and by exacerbations of inflammation in the edematous areas following inoculations with staphylococcal or streptococcal filtrates. Although these patients have shown a general sensitization to the toxins and products of streptococcus and staphylococcus, the diseased areas have been found especially sensitive. Since vaccines prepared in various ways failed to help patients with infectional edema, filtrates were tried. This method of treatment was successful. During treatment with filtrates from cultures of staphylococcus or streptococcus, local reactions in the diseased area occurred frequently as the dose was increased, but all patients eventually tolerated large doses, and inoculations were discontinued without recurrences of infection. Both hyposensitization and increased immunity apparently resulted from the treatment. While the only bacteria causing infectional edema are staphylococcus and streptococcus and the sensitizations are permanent; according to the studies made so far, any one or all of the upper respiratory pathogens may be responsible for attacks of asthma and the sensitizations are transient. Regardless of the variable flora and sensitizations occurring in infectional asthma, the markedly successful results with filtrates in the patients with edemas justified the treatment of asthmatic patients with filtrates selected and combined to satisfy the varying flora and sensitizations.

The filtrates used for the treatment of chronic infectional edema were prepared from four-day cultures of autogenous strains of *Staphylococcus aureus* and of *Streptococcus hemolyticus* or from toxin-producing stock strains of these bacteria for patients from whom autogenous strains were not obtained. Flasks of 2 per cent proteose peptone beef infusion broth were seeded heavily and filtered at the end of the fourth day of incubation. At this time the toxin production in this medium in a normal atmosphere is usually at its height, and the bacteria have already undergone partial autolysis. Filtrates prepared in this way contained appreciable quantities of toxins and of autolytic products, both capable of causing reactions in the human skin. The cutaneous

reactions caused by the toxins in these filtrates do not occur if streptococcal or staphylococcal antitoxin is added to a toxic filtrate before the intradermal inoculation. With filtrates containing these neutralized toxins, the residual reactions resembled the reactions obtained with the nucleoprotein fractions of the bacterial bodies and occurred only in patients who were sensitive to the nucleoproteins of these bacteria. The first filtrates used for the treatment of infectional edema were carefully titrated for toxin content, but subsequent experience showed that the toxicity of a filtrate did not depend entirely on the strength of toxin in a filtrate but to a large extent on the sensitivity of the patient to the autolytic decomposition products. The latter sensitivity varied so widely with different patients and at different times during the course of treatment that no standardized dosage or series of doses could be predetermined, so each patient was first given a small amount of a highly diluted filtrate, and the doses were then increased by such amounts as the patient could tolerate without focal or constitutional reactions. Inasmuch as the titration of the toxins was not helpful in determining the dosage which could be tolerated, accurate titrations of the toxins were subsequently abandoned. The method used for preparing these streptococcal and staphylococcal filtrates was adapted to the preparation of the filtrates used for inoculating the children with infectional asthma. Cultures have been made on blood-agar plates, and the isolated bacteria suspected of pathogenicity have been transferred to tubes of blood broth, then to flasks of proteose peptone broth. Usually these broth cultures have been grown four days before filtration. Recently influenza bacillus has been grown symbiotically with *Staphylococcus aureus* to avoid the introduction of growth accessory substances to the cultures. In these symbiotic cultures the influenza bacillus autolyzes early during growth so the cultures have been filtered as soon as stained films have shown beginning autolysis of the bacillus. Equal parts of each of the filtrates from cultures of the bacteria found in the original plates have been added to equal quantities of stock filtrates from cultures of the other upper respiratory pathogens not present in the respiratory tract when the cultures were made, so that the final mixture has usually contained equal parts of filtrates from cultures of all six of the bacteria mentioned as commonly prevalent in the respiratory tract during infection. This sterile mixture has been preserved with 0.5 per cent phenol, appropriately diluted, and used for treatment.

DOSAGE

The usual initial dose of filtrate has usually been 0.1 c.c. of a 1:100 dilution. In this dilution when six bacterial filtrates were included in the mixture the dilution of each has been 1:600, a dilution suffi-

ciently high that the mixture contained minimal doses of staphylococcal and streptococcal toxins even though the filtrates were prepared with strongly toxigenic strains. There have been no severe local or general reactions to this initial dose. The subsequent doses have depended entirely on the tolerance of the patient. With increasing dosages four varieties of reactions have been observed: first, chills and fever lasting one or two days (three instances); second, excessive swelling at the site of the inoculation; third, transient attacks of asthma occurring from six to twelve hours after an inoculation (observed in thirty-four of the children at some time in their series of treatments); fourth, an almost continuous asthmatic state induced by repeated overdosage (three instances). These reactions have occurred even though the doses given have always been considered well within the tolerance of the patients. Apparently they cannot be entirely avoided because of the fluctuation in the sensitivities of the patients to the bacteria represented in the filtrates. Each time a reaction has occurred, the dose has been reduced to one within the tolerance of the patient, then gradually increased. All the patients who have had reactions have eventually tolerated large doses. During the first few months inoculations have been given twice each week with increasing doses of dilutions of 1 to 100, 1 to 50, and 1 to 20 of the original filtrate. Ten of the patients had almost continuous asthma which ceased after several weeks of inoculations given twice each week, but the asthma recurred when the injections were given at longer intervals. When the patients could tolerate inoculations of 0.1 c.c. of undiluted filtrate the dose has been increased by 0.1 c.c. with each inoculation until 1 c.c. of the original filtrate could be given; then this dose was continued at intervals of one or two weeks. During the first year of treatment all patients have been given weekly inoculations after the full dosage was reached until the beginning of the summer. Since forty-four of these patients had asthma only during the winter, they were treated only during the fall and winter months. The others (nine) had asthma at times during the summer and were given inoculations through June and July as well. Each fall fresh filtrates have been prepared for each patient and inoculations given each successive year until the patient was free from asthma during an entire winter.

DISCUSSION AND SUMMARY

Fifty-three children with infectional asthma have been treated with gradually increasing doses of filtrates of cultures of the common upper respiratory pathogenic bacteria. On account of the extreme variations in the bacterial flora of the respiratory tract in consecutive attacks of asthma and the constantly changing cutaneous reactions to the nucleoproteins of these bacteria, filtrates of cultures of bacteria found

in the respiratory tract have been prepared, and filtrates of other pathogens not found when the cultures were made have been added. After persistent treatment with these filtrates fifty of these children appear well. It cannot be said, however, that they are permanently cured because specific sensitizations may develop later and infectional asthma may recur. In fact some children have apparently developed specific sensitizations to pollens and foods while under treatment for infectional asthma and so were excluded from the purely infectional group. Filtrates were used in treating these patients because they had been effective in immunizing and desensitizing patients with chronic infectional edema, a disease in which bacterial vaccines prepared by several methods were not curative. The method of selecting the bacteria used in preparing the filtrates is by no means perfect because bacteria not represented in the filtrates probably invade the respiratory tract at times, but such errors can be obviated to some extent by frequent studies of the respiratory flora in patients not benefited by treatment. Since attacks of asthma have occurred in many of these patients following inoculations, some degree of specificity must be attributed to the preparation used in treatment, even though passive transfers have not ordinarily been obtained with the serum of these patients on testing with the proteins of the bacteria represented in the filtrates. Apparently the satisfactory results obtained with this method of treatment are largely specific because patients with specific sensitizations have not been entirely relieved by treatment with filtrates until the specific causes have been discovered and appropriate treatment instituted. So far these filtrates have not been as satisfactory in the treatment of adults as in the treatment of children, and it must be admitted that the group presented represents a type of asthma which responds favorably to treatment. At the present time some of the factors which render the adult patient more resistant to filtrate therapy and various modifications of the method used for preparing the filtrates are under investigation.

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DIFFERENTIAL DIAGNOSIS OF NONRHEUMATIC "GROWING PAINS" AND SUBACUTE RHEUMATIC FEVER

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MUCH has been written concerning the significance of muscular and joint pains in relation to childhood rheumatism. We are repeatedly reminded in this literature that rheumatic fever is protean in nature and that children with such pains need to be carefully studied for possible rheumatic infection. Such painful extremities have been given a variety of names by various authors; some have labeled them "growing pains," and others "growing and joint pains"; while "muscular rheumatism" and "fleeting joint pains" have also been used to designate the same symptom. Growing pains are now considered by many[1] a major manifestation of rheumatic fever along with acute polyarthritis and chorea. In recent statistical studies,[2] from 8 to 50 per cent of children considered to be suffering from rheumatic fever are so diagnosed on the basis of a history of growing pains alone. On the other hand, using the questionnaire method, one investigator[3] found that 7.1 per cent of 48,000 normal school children complained of pains in the extremities, while another[4] found 21 per cent of 208 school children with the same complaint. Study of these recent reports reveals that there is considerable confusion on this whole subject. The difficulty has been, I believe, that healthy children complaining of nonrheumatic pains have been mistaken for patients suffering from subacute rheumatic fever. This report is an attempt to clear up this confusion and to point out the differences between these two groups of children.

It is of interest to go back into the earlier literature and to trace the development of the modern ideas on the subject of growing pains. In the eighteenth and early nineteenth centuries, a constant debate was carried on by writers as to whether or not growth was painful. Many investigators were of the opinion that because such symptoms were prevalent during the growing period, the pain was due most likely to engorgement of the epiphysis, which accompanies normal growth. At that time, students of rheumatic fever, however, did not consider growing pains, a symptom of this disease. Cheadle and Church[5] in describing mild attacks of childhood rheumatism discuss only definite joint pains involving numerous joints of the body, the type of joint pain which comes on mostly on motion. Garrod[6] in his classical monograph on rheumatic fever writes: "The question at once arises whether mere articular pains are correctly described as rheumatic symptoms. They probably are, but

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only those pains which can be distinctly located in the joints should be so classed." It is important to note that Garrod stressed the significance of joint pains particularly.

The present conception of growing pains developed mostly from several statements made by Jacobi. As happens not infrequently in medical literature, an opinion given by a recognized authority is sometimes accepted without the usual critical analysis. Unfortunately, the exact implication of such opinions is not always understood, and they are often exaggerated and distorted to fit in with a certain point of view. Jacobi[7] did state in one of his many papers, "The large majority of attacks of growing pains means rheumatism." It was the acceptance of this point of view which led physicians more recently to consider all leg pains in children as probably rheumatic, and yet Jacobi[8] later stated: "In many instances growing pains are but the expression of muscular fatigue." But not all modern writers have confused growing pains with mild rheumatic polyarthritis. Pollack[9] in Abt's Pediatrics writes: "In growing children, especially girls, from two to ten years of age and often about the age of puberty, weakness, stiffness, and pains in the muscles are occasionally observed. Usually they occur at night or towards evening. When they come on during the night, the child is awakened by pains in the thighs or legs, so severe that they cause the child to cry out. After a time the pain subsides, and the child again falls asleep, frequently to be awakened again by the pain either in the same place or in another extremity. Finally the pain disappears, and the next morning the child is as well as ever. These pains recur at varying intervals, about once a week or less frequently. They rarely affect the arms. The changes incident to growth in the upper epiphysis of the tibia and the lower epiphysis of the femur have been suggested as an etiologic factor." This essentially expresses my point of view.

Considerable experience with children attending our heart clinic has led me to conclude that the great majority of children with pain in the extremities are not suffering from rheumatism and should not be classified as potential cardiac patients. It will be found that a large number of normal children have severe muscular pain in their extremities throughout childhood and through the adolescent period. Such children do not present the symptoms characteristic of rheumatic disease and do not develop heart disease. It is true that a small number of children with well-defined rheumatic heart disease give a history only of joint pains, but it will be shown that their symptoms differ decidedly from those children who have what I prefer to designate as growing pains.

Before discussing our findings on the children with growing pains, I wish first to consider the histories of 100 of our patients, chosen at random, who had well-developed rheumatic heart disease. It has been stated by many writers that only about 50 per cent of patients with rheumatic heart disease give a definite history of acute polyarthritis or

chorea and that the rest of them give a vague history of muscular rheumatism or so-called growing pains. It was my purpose in examining these histories to determine how often it was necessary to accept a story of growing pains alone to explain the development of unquestioned rheumatic heart disease. These histories were carefully obtained soon after the onset of the disease, and all of these patients have been under my personal observation for a number of years.

It will be noted (Table I) that of these 100 cardiac children, 84, or 84 per cent, gave histories of definite attacks of acute polyarthritis or chorea, or both. Sixty of them had rheumatic fever alone; 8 had chorea alone; and 16 had both rheumatic fever and chorea. These episodes include only major manifestations of rheumatic fever sufficiently severe in almost every instance to put the patient to bed either in the home or in the hospital. Sixteen patients, or 16 per cent, however, gave no history of an attack of either acute polyarthritis or chorea.

TABLE I

100 CASES OF RHEUMATIC HEART DISEASE

ACUTE POLYARTHRITIS	ACUTE POLYARTHRITIS AND CHOREA	CHOREA	NO HISTORY OF ACUTE POLYARTHRITIS OR CHOREA	TOTAL WITH DEFINITE ATTACKS OF RHEUMATIC FEVER
60 (60%)	16 (16%)	8 (8%)	16 (16%)	84 (84%)

Of the 84 patients with a definite history (Table II), 58 had mitral disease; 3 had aortic disease; while 23 had both mitral and aortic lesions. Of the 16 without definite attacks of rheumatic fever, 9 had mitral disease; none had aortic disease alone; while 6 had both mitral and aortic disease; and 1 had adhesive pericarditis. Continuous observation of these patients was made in the clinic, convalescent hospital, and special school.

TABLE II

DIAGNOSIS AND X-RAY EXAMINATION

	NUMBER OF CASES	DIAGNOSIS			
		MITRAL	AORTIC	MITRAL AND AORTIC	ADHESIVE PERICARDITIS
Definite attacks of acute polyarthritis, or chorea, or both	84	58 (69.0%)	3 (3.6%)	23 (27.4%)	0
No definite attacks of acute polyarthritis or chorea	16	9 (56.3%)	0	6 (37.5%)	1 (6.3%)

It will be noted (Table III) that the great majority of them suffered further rheumatic symptoms. Of the 84 patients with definite rheumatic history, 56 had further joint pains; 43 had frequent severe nosebleeds; while 60 had further involvement of the joints of the upper extremities.

Twelve had skin rashes considered characteristic of rheumatic fever. Of those patients without definite history, 6 continued to have further joint pains; 3 had severe nosebleeds; and 5 had involvement of the joints of the upper extremities. As far as the lesions in the heart or the nature of the continued rheumatic process is concerned, no difference could be noted between those children who suffered a definite major manifestation or rheumatic fever and those who did not.

TABLE III

FURTHER RHEUMATIC SYMPTOMS DURING OBSERVATION PERIOD

	NUMBER OF CASES	FURTHER JOINT PAINS	PAIN IN JOINTS OF UPPER EXTREMITIES	NOSE-BLEEDS	SKIN RASH
Definite attacks of acute polyarthritis or chorea	84	56 (66.7%)	60 (71.4%)	43 (51.2%)	12 (14.3%)
No definite attacks of acute polyarthritis or chorea	16	6 (37.5%)	5 (31.3%)	3 (18.8%)	0

On taking the usual routine histories alone, it might be concluded that these 16 patients had nothing more than growing pains or so-called "vague history of muscular rheumatism." Yet on closer questioning, it was found that 10 of them gave histories quite typical of subacute rheumatic fever; 4 of primary carditis; while only 2 gave no such rheumatic history. Of those with subacute rheumatic fever, the following three excerpts from their histories are typical.

(1) "About four years ago, had stiffness in hips and knees and in muscles of thighs—not confined to bed but out of school a month—unable to walk stairs because of pain in joints."

(2) "Two years ago, just after having had measles, developed pain in knees and ankles; joints were not swollen but was unable to walk without pain for three weeks, during which time was absent from school; seven months later, during school physical examination, mitral disease was discovered."

(3) "For past two or three years has complained of pain in various joints; patient points out pain definitely in joints. Pain occurred in knees, elbows, shoulders; mother states patient has unexplained fever from time to time; was once confined to hospital for two weeks with fever of undetermined origin."

Typical of the four patients with primary carditis are the following excerpts from their histories.

(1) "First became ill early this spring; complained of fatigue; had low-grade fever; examined by family physician who diagnosed active carditis for which patient was confined to hospital for two months."

(2) "Admitted to hospital with fractured radius; developed acute tonsillitis with high fever; fever continued for next six weeks, during

which time a blowing systolic murmur was discovered at apex; while under further observation, continues to have active carditis with increasing damage to heart."

As will be pointed out, such histories are not those of patients with growing pains; they are rather typical of children suffering from rheumatic fever. It is possible that the two patients without any rheumatic history could have had active, unrecognized primary carditis. It can be concluded then that, when careful histories are obtained from patients with rheumatic heart disease, a positive history of rheumatic infection will be obtained in almost every instance.

To emphasize my point of view, I should like to point out the characteristic symptoms in children with nonrheumatic growing pains. These children were referred to the clinic for cardiac examination by physicians and nurses because it was thought that they were suffering from rheumatic fever. Many of them had received various types of treatment, including tonsillectomy and sinus drainage. In some instances, they had been kept in bed for weeks because of the supposed rheumatic infection. Frequently, when such children were found to have a murmur in the heart, a diagnosis of rheumatic heart disease had been made. I find that these children give histories which are strikingly similar. They are well nourished, healthy children who not uncommonly come from families in the upper economic levels. They point out the location of their pain in the muscles of the legs and thighs and rarely have pain in the upper extremities. Pain usually begins at the end of the day and is most severe about two hours after they have fallen asleep. They are awakened several times during the night, and the parents relieve them of their distress by applying heat, massaging the muscles, or giving them aspirin. In the morning they are free of pain and stiffness but may be tired because of disturbed sleep. They seldom are absent from school because of this complaint.

On following this group of patients, I find that they do not develop any of the other well known symptoms of rheumatic infection, such as severe nosebleeds, skin rash, joint pains, or fever. The sedimentation rate and leucocyte count are invariably normal. The complaint of leg pains continues both through summer and winter, and there does not seem to be any relation to change in weather. Their symptoms continue over several years and usually disappear after adolescence. A history of other cases of rheumatic fever in their families is uncommon. On repeated examinations over a period of years, it is found that they do not develop rheumatic heart disease.

Contrast this picture with the symptoms found in children suffering from subacute rheumatic fever, children with repeated attacks of joint pains like the patients mentioned above. They commonly develop their symptoms after an upper respiratory infection or after one of the contagious diseases. They complain of pain in the joints themselves, in-

volving both the upper and lower extremities. Pain is brought on especially by motion. They are commonly undernourished and come from families of the lower economic levels. On first getting out of bed in the morning, they complain of pain and stiffness on motion. It takes them some time before they can walk about freely, and they often limp. The pain is present more or less during the entire day but gradually disappears after getting warm in bed. Examination of the painful joints will not infrequently reveal local heat of moderate degree and even mild swellings which were overlooked by the parents. Nosebleeds, skin rash, fever, increased sedimentation rate, mild leucocytosis, as well as mild anemia, are common in this group. Even when they are not complaining of joint pains, many of them will be found to have a low-grade fever. In other words, they present all the symptoms of a persistent long continued low-grade infection. Other cases of rheumatic fever in their families are common. As is well known, many of these patients gradually develop valvular heart disease while under observation. We have then, on the one hand, a group of healthy children who complain of leg pains, especially at night, while on the other hand, we are dealing with sick children who have all the symptoms of a chronic infectious disease.

TABLE IV

DIFFERENCES BETWEEN NONRHEUMATIC "GROWING PAINS" AND JOINT PAINS OF SUBACUTE RHEUMATIC FEVER

	NONRHEUMATIC "GROWING PAINS"	JOINT PAINS OF SUBACUTE RHEUMATIC FEVER
Age at onset	Early childhood—often continues through adolescence.	Most commonly between six and seven years of age—often occurs in attacks following upper respiratory infections or other infectious diseases.
Time of pain	At end of day—especially during night often awakening the child several times. Pain is gone in the morning and usually does not occur during the day.	On first getting out of bed in the morning—during entire day—especially on motion; often causing limp. Patient feels better on getting warm in bed.
Location of pain	Most commonly in muscles of legs and thighs—rarely in muscles of upper extremities. Occasionally involves knee joints.	In the joints themselves of upper and lower extremities.
Other signs of rheumatic activity	Usually none.	Repeated bouts of joint pains; nosebleeds, characteristic skin rash, pallor, fever, etc.
Objective signs in joints	None.	Joints often have slight increased local heat and mild swelling usually overlooked by patient and parent.
Family history of rheumatic fever	Uncommon.	Common.
Laboratory findings	Normal sedimentation rate. Normal leucocyte count. Normal hemoglobin.	Increased sedimentation rate. Mild increase in leucocyte count. Moderately decreased hemoglobin.

In a smaller group of patients who complain of painful extremities, a clear-cut differentiation cannot be made. They have symptoms which suggest both the muscular pain of growing pains and specific joint pain as well, together with some signs of infection. Such children need to be observed over a period of time before a definite diagnosis can be made.

In the vast majority of cases, however, a clear-cut differentiation can be made, and those with nonrheumatic growing pains alone, who do not develop heart disease, can be separated from those with subacute rheumatic fever. From these observations, I have worked out the following clinical differential diagnostic chart (Table IV) which I believe will be of assistance.

DISCUSSION

Until the etiology of rheumatic fever is discovered, it will be necessary to make a diagnosis on the clinical picture. A number of tests have been tried as diagnostic measures in recent years, such as skin tests, artificial production of rheumatic nodules, and other complicated bacteriologic procedures, but none of them have proved of practical value. It is of importance, then, to understand clearly the various clinical manifestations of the rheumatic state. In our anxiety to diagnose rheumatic infection at the earliest possible moment, it is my opinion that many children have been incorrectly considered as rheumatic patients and have been so treated. I believe that one reason for this error is due to the teaching of many investigators who find that only about 50 per cent of their patients with rheumatic heart disease give a history of rheumatic infection. It may be a fact that many adults forget mild attacks of rheumatic disease they may have had in early childhood. It is also well to remember, too, that adults with rheumatic heart disease most probably had their initial rheumatic infection between twenty and thirty years ago, when this disease was not so well understood. However, in the group under consideration consisting of children and young adults, a positive history can be obtained in almost every instance when careful histories are taken. Unfortunately, this takes the time and effort of an examiner who is well informed on this subject and cannot be left to a clerk or even an intern.

Some of the confusion would be overcome if the term "growing pains" were not used in connection with rheumatic fever. I have described a clinical entity which I have called growing pains and which I am certain is not due to the rheumatic infection. I do not, however, mean to imply that all children with painful extremities are included under this heading. It is understood, of course, that painful extremities may be produced by a variety of orthopedic and muscular abnormalities. I have inferred that the clinical syndrome labeled "growing pains" may be due to normal physiologic growth. This is nothing more than speculation as I have no facts to support this point of view. Whether or not normal growth is painful remains to be proved.

CONCLUSIONS

There is a distinct clinical difference between nonrheumatic growing pains and subacute rheumatic fever.

Growing pains are not due to the rheumatic infection, and children with such pains do not develop rheumatic heart disease.

Virtually all patients with rheumatic heart disease, especially children and young adults, give a positive history of rheumatic infection.

The important differences between nonrheumatic growing pains and subacute rheumatic fever have been described, and a differential diagnostic chart is included.

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EPIDEMIC ENCEPHALITIS TYPE B IN CHILDREN

Clinical Observations in the 1937 Outbreak

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IN THE summer of 1937, four years after the first outbreak and exactly as expected epidemiologically, encephalitis type B reappeared in the St. Louis area. This epidemic was not so serious as that of 1933, inasmuch as the total incidence remained considerably below the figures for 1933. In almost every other respect it followed the same course as that of 1933.

Comparative figures for the two epidemics are given in Tables I and II. These figures are taken from the final report of the Health Division of the City of St. Louis and apply to residents only.

Table I

	1933 (575 cases)	1937 (338 cases)
Incidence by Age		
0- 9 yr.	46 (8.0% of total)	28 (8.2% of total)
10-19 yr.	53 (9.2% of total)	24 (7.1% of total)
Case Fatality Rates		
All ages	22.5	26.3
0- 9 yr.	6.5	10.4
10-19 yr.	5.6	12.5

Table II

Comparative Rates Per 100,000 Estimated Population

	Cases		Deaths	
	1933	1937	1933	1937
All ages	69.0	39.5	15.5	10.4
0- 9 yr.	38.0	23.1	2.5	2.5
10-19 yr.	34.2	19.0	2.4	2.4

In the St. Louis Children's Hospital twenty-four children were admitted with the diagnosis of encephalitis type B during the months June to October, 1937. The statistical tabulation of this material follows, showing the epidemiology (twenty-four cases):

Sex:	Male	18	Age: 0- 1 yr.	5
	Female	6	1- 5 yr.	2
			6-10 yr.	15
			11-15 yr.	2

Residence:	City	17	Onset by month:	June	1
	County	4		July	1
	Other	3		August	11
				September	9
				October	2

Onset with:	Upper respiratory symptoms	15
	No upper respiratory symptoms	9

Residual signs:	Some	3	Symptoms:	Meningeal	24
	None	21		Stupor	11
				Personality change	13
				Muscle palsy	7
				Convulsions	8

DISCUSSION

Epidemiology.—It is interesting to note that the incidence in male children was three times as high as in females in our material, although this does not hold true for the other figures.

None of the children died in the hospital, but one child who had epilepsy and showed severe defects of the central nervous system preceding the onset of encephalitis died two months later. Death probably was due indirectly to encephalitis.

Five of the children were under one year of age, and one was only four months old. Incidence was highest in the age group of 6 to 10 years, almost two-thirds of the patients belonging in that quinquennium.

The peak of the epidemic was reached at the end of August, with a sharp decline in the second half of September.

Symptomatology.—Onset: This was usually sudden and as a rule did not manifest anything characteristic. The great majority of the children showed symptoms of a mild upper respiratory infection, making it appear likely that invasion occurred through the nasal route. The prodromal stage lasted from twenty-four to seventy-two hours, after which apparently the central nervous system was invaded. With the stage of invasion the general systemic reactions became more severe, and the symptoms soon pointed to an involvement of the nervous system. There was marked prostration in almost every case. The children showed signs of great discomfort.

In the very young children this was evident only from their general behavior, while the older children complained very early of intense headache. The headache was not localized to any area but was diffuse. This suffering continued until a gradually increasing disturbance of consciousness sooner or later led to a state of somnolence or deep stupor. But even during this stage there were periods of great rest-

lessness, apparently due to headaches. With the beginning of disturbance of consciousness, the face of the patient assumed a blank staring expression. This seemed to be a more or less unique feature of the disease. The facial expression of these young patients was rather characteristic and was unlike the rigid face of encephalitis A.

The temperature curve varied greatly. There was either a sudden or a gradual rise. Maximal temperatures ranged up to 38°-40° C. or even higher. The curve, as a rule, was continuous for several days or weeks. The most prolonged curve in our series lasted over twenty days, but the average duration was about nine or ten days. The temperature as a rule decreased gradually.

The pulse and respiratory rates without exception were in proportion to temperature and did not show any peculiarities.

The great organ systems did not show any reactions or symptoms which would not be consistent with a severe generalized infection and with a disturbance of consciousness. Feeding of the children in the unconscious state placed heavy demands on nursing but in no instance was there any need for forcible or parenteral administration of food. Parenteral injection of glucose or other fluid was resorted to in a few instances, but more for reasons of therapy than for maintenance of nutrition.

Central Nervous System: As soon as the stage of invasion began, the clinical picture was dominated by symptoms and signs pointing to a diffuse involvement of the central nervous system. The disturbance of consciousness as described above lasted from a few hours up to fifteen to twenty days. In about 50 per cent of the patients it reached the degree of stupor, while in the others it was less severe. Together with the somnolence or stupor there was naturally a noticeable change of personality and of behavior. This change as a rule followed a parallel course with the disturbance of consciousness, but often it continued much longer. In many instances a changed reaction of personality in the form of lassitude or irritability outlasted the acute stage. The question whether any permanent change of personality remained in any of our patients may be answered only through later investigation and follow-up.

Signs of meningeal irritation were present in all of our patients. Rigidity of the neck was evident in every one, and in a good many of them there was also rigidity of the back. Kernig and Brudzinski signs could be demonstrated at the height of meningeal involvement in every case.

Convulsions of the tonicoclonic type occurred in eight patients. The attacks occurred approximately at the time of invasion of the central nervous system. They consisted either of a short series of convulsions or only one single seizure. In no instance did the convulsions reoccur in the later stages of the disease.

In seven patients mild transient muscle paralyses were noted. They usually appeared in the form of monoparesis or hemiparesis, accompanied by the usual signs of an upper motor neurone lesion. They did not last longer than a few days, and then complete recovery followed.

Changes in reflexes were noted only with the transient pareses. The abdominal reflexes were, as a rule, absent during the stage of meningeal irritation.

The eyegrounds did not show any change with the exception of one patient in whom a questionable choking of the disks was present for a short time.

Clinical Pathology: The white blood cell count ranged from 4,050 up to 28,600. It presented the usual infectious picture with a more or less pronounced shift to the left. Beyond this nothing characteristic was noted.

Chemical studies of the blood were done in ten cases but only for sugar. The figures range from 46 mg. per cent to 164 mg. per cent, the mean being 110 mg. per cent.

The cerebrospinal fluid showed very definite changes. Lumbar puncture was done in every case and in several patients two or three times. Altogether forty-nine studies of the cerebrospinal fluid are on record giving an average of two per patient. The pressure in the lumbar needle was apparently increased in every instance, but no manometric measurements were made.

The cell count ranged from one cell to 850 cells. The average count was 110 and the mean count 70. The count varied greatly in the same patient. It showed a gradual increase in the first few days and a slow gradual decrease afterwards. The highest cell count was found between the fourth and eighth day after onset.

The character of the cells also varied depending on the day on which the cerebrospinal fluid was examined. The proportion between segmented (P) and mononuclear (L) cells in the first three days was P/L 90/10, 50/50, 40/60. After the fourth day it changed to P/L 10/90, 2/98, 0/100.

Protein content as determined by the Pandy test was variable. In twenty-nine instances it showed a definite increase, while in twenty specimens there was no increase.

There was no parallelism between high cell count and protein content, but the two showed definite dissociation.

The only other chemical test done was for sugar content, which varied between 32.8 and 103 mg. per cent, the mean being 75 mg. per cent.

Serologic Studies: Neutralization tests on white mice were carried out with several sera obtained from our patients. In many of these, neutralizing substances were demonstrated. These studies were made

by Dr. Margaret Smith, of the Washington University Medical School, Department of Pathology, and a report has been published in the *Journal for Infectious Diseases.*

Diagnosis: During an epidemic, as at the time when our observations were made, it should not be difficult to make the diagnosis of encephalitis B. More difficulty will be encountered in sporadic cases or at the beginning of an epidemic. It is probable that many of the mild or abortive cases will go unrecognized even during an epidemic or will be classified under some other label.

On the other hand, history carefully taken and the characteristic clinical picture as described will inevitably suggest the possibility of encephalitis B to the careful observer. The rather sudden onset of meningeal irritation accompanied by severe headaches and the very early disturbance of consciousness are so characteristic that they may be justly considered as almost peculiar to this disease.

Definite diagnosis, of course, may not be established without laboratory examination of the cerebrospinal fluid. In the prodromal stage unfortunately no reliable laboratory tests are available. After the period of invasion sufficient changes will be present in the cerebrospinal fluid to make the diagnosis of encephalitis B possible, and often rather easy. Pleocytosis in the cerebrospinal fluid is very characteristic, and it may reach high figures. After four or five days the mononuclear cells predominate. Protein content may be increased, but it is as a rule dissociated from pleocytosis. An important diagnostic criterion is the absence of organisms in smears and in cultures.

Differential Diagnosis: Meningitis has to be considered only in its acute forms as produced by various bacteria. The clinical picture of encephalitis B although manifestly colored by meningeal involvement is dominated by the early disturbance of consciousness. In meningitis, with the exception of the fulminant forms, the meningeal irritation predominates, and the disturbance of consciousness may follow later. This difference is evidently due to the variation in the pathologic process and in the sequence of involvement of brain tissues.

The cytology of the cerebrospinal fluid is usually helpful in ruling out meningitis, particularly if mononucleosis predominates. More important will be of course the absence of microorganisms in the fluid.

Lymphocytic choriomeningitis in children has been almost unknown in St. Louis and therefore did not have to be considered in the differential diagnosis at this time.

Encephalitis A will hardly ever be confused with Type B. The absence of meningeal involvement, the less acute onset, the more protracted course, the very pronounced predilection of the virus for the basal ganglia with the resultant, extrapyramidal and other related syndromes mark that disease very sharply as an entity.

Postinfectious encephalopathies or disseminated encephalomyelitis may lead to a disturbance of consciousness lasting from a few hours to several days. On the other hand, meningeal signs and changes in the cerebrospinal fluid will be absent or insignificant. Besides there is a much more pronounced tendency to focal involvement in those cases than in encephalitis B.

Poliomyelitis may cause more difficulty in differential diagnosis than all the other diseases combined. In epidemiologic behavior the two diseases are very much alike. In geographic distribution and in seasonal incidence they overlap. These difficulties multiplied for us in St. Louis in 1937 because in that year we witnessed together with the encephalitis epidemic the worst outbreak of poliomyelitis in fifty-seven years. The result was that in at least four instances a mistaken diagnosis of encephalitis B was made and later corrected to that of poliomyelitis after the appearance of muscle paralyses.

In the prodromal stage it is impossible to differentiate between the two diseases. At present no laboratory test is available that would make such a decision possible. The same holds true in the early phase of invasion of the central nervous system or in the so-called preparalytic stage of poliomyelitis. Here the laboratory tests and even the most careful and minute studies of the white blood cells or the cerebrospinal fluid will fail. Careful clinical observations of the behavior of the patient and of a possible disturbance of consciousness will be much more helpful. In poliomyelitis there is very little likelihood to find any disturbance of consciousness while in encephalitis B this is the almost inevitable rule.

Unfortunately also the so-called neutralization tests on mice will fail us in the early diagnosis. They require many days for the results. Besides they are of value only in case of a previous attack of encephalitis B, when they show positive results. Immune bodies do not appear until much later, and therefore neutralization tests are of no help in the early phase of a recent infection with encephalitis B virus.

After evidences of a lower motor neuron lesion appear, the need for differential diagnosis, of course, ceases to exist.

Prognosis in children seems to be generally favorable. All of our patients, with the exception of a previously defective epileptic child, recovered completely. No residual signs were noted or reported up to the time this paper was written.

Treatment was purely symptomatic. No specific measures for treatment are available. Careful bedside nursing was required in every patient because of the disturbance of consciousness. Feeding of these children particularly taxed the nursing staff. Routine methods in treatment did not differ in any important point from those used in other severe general infections. Fluids were forced orally and occasionally glucose or Hartmann's solution was given subcutaneously or intra-

venously. Few drugs were used, but occasionally antipyretics were given. Sulfanilamide was tried in a few instances without any appreciable result.

ENCEPHALITIS B (CASE REPORTS)

CASE 1.—P. M., female, aged 13 months, was admitted Sept. 11, 1937. The previous day she suddenly developed high fever and had a convulsion lasting thirty minutes followed shortly by another severe convulsion lasting one hour. She was improved somewhat the next morning and played. In the afternoon the temperature rose again, and she became drowsy. She had another attack of convulsions lasting fifteen minutes.

On admission the temperature was 38.9° C.; the child was acutely ill, listless and flaccid. Respirations were slow and shallow. There was a lateral nystagmus; pupils were small and reacted to light. The neck was slightly rigid; no Kernig sign; jaws were held tightly closed. The right leg was spastic, other extremities were flaccid. Abdominal reflexes were absent; deep reflexes, hyperactive.

On admission the cerebrospinal fluid showed increased pressure, 35 cells with 92 per cent lymphocytes; Pandy test was positive; no organisms were seen or cultured. Two days later the pressure was down, and there were 75 cells with 90 per cent lymphocytes. Two weeks later 51 cells were yet present in cerebrospinal fluid.

The temperature remained rather high for a week and returned to normal in about thirteen days. This child also had spastic paralysis of the left side. Facial expression was vacant; she gritted her teeth continually. Mentality appeared somewhat inferior. She was in the hospital three weeks.

CASE 2.—S. E., a 6-month-old boy, was admitted Oct. 15, 1937. Previously he was a perfectly normal healthy infant. Two days before admission he developed a high fever, refused to eat, and showed mild signs of an upper respiratory infection. Fever, restlessness, and anorexia increased. A few hours before admission he had generalized convulsions lasting a few minutes.

On admission the temperature was 39.2° C., and the baby was very drowsy, looked flushed, and acutely ill. Anterior fontanel was tense, but not bulging. Some nuchal rigidity and stiffness of back were present.

Temperature rose to 40° C. and above during the next two days and then came down gradually and reached the normal line in seven days. The condition improved gradually, consciousness returned and nuchal rigidity disappeared.

Cerebrospinal fluid on admission was clear, had 350 cells in 1 c.c., 40 per cent polymorphonuclears and 60 per cent lymphocytes. The Pandy test was negative. The following day the count was 170 with 56 per cent lymphocytes; two days later 50 cells were counted with 90 per cent lymphocytosis. The Pandy test remained negative.

This baby was given parenteral fluids repeatedly; phenobarbital and aspirin also were administered at times.

CASE 3.—D. G., male, aged 13 months, was admitted Sept. 13, 1937. This baby was apparently in excellent health until the day before admission. On that morning it was noted that he was rather hot and listless. Temperature remained high, and baby vomited several times. On the next afternoon he had a severe attack of convulsions lasting about 45 minutes.

On admission the temperature was 38.5° C. He looked acutely ill and was unconscious. Bloody vomitus came from mouth; face, arms, and legs twitched somewhat. His neck was not stiff; no Kernig sign was present. Abdominal reflexes were absent, but all deep reflexes were active.

TABLE

REPORT OF CASES OF ENCEPHALITIS IN THE ST. LOUIS

NO.	HISTORY	SEX	AGE	DATE		PREDOMINATING SYMPTOMS				SPINAL FLUID				
				ONSET	ADM.	IRRITATIVE MENINGEAL	STUPOR	MUSCLE PALSIES	PERSONALITY CHANGE	D.*	CELLS	P/L	PROTEIN	SUGAR
1.	H2488	M	6 yr.	6/27	6/28	+	0	0	0	1 6 10	4 250 32	-- 50/50 1/99	0 + 0	57.5
2.	I 650	F	6 yr.	7/14	7/19	+	0	+	0	5 10	15 32	2/98 2/98	+ +	49.6 32.0
3.	N1409	M	4½ yr.	8/ 6	8/ 7	+	0	+	+	1 4	7 100	-- 40/60	0 +0	95.8
4.	M 324	M	13 yr.	8/15	8/18	+++	+++	++	+++	5 8 24 30	193 184 42 16	30/70 -- 20/80 4/96	++ +0 +0 +0	98.0
5.	N1507	M	6 yr.	8/16	8/19	+	+	+	+	3	163	22/78	+	
6.	N1504	M	10 yr.	8/16	8/19	+	0	0	+	3 6	200 46	25/75 --	+ +	58.0
7.	H 338	M	6 yr.	8/21	8/22	+	0	+0	+	1 bloody tap 4	5	--	0	
8.	N1548	M	8 yr.	8/21	8/24	+	+	0	0	3	143	34/66	+	
9.	I 837	M	9 yr.	8/17	8/26	+	0	0	0	9 12	70 59	40/60 60/40	++ +0	
10.	N1584	M	5½ yr.	8/26	8/29	+	++	0	+	3	290	80/20	+0	
11.	N1604	M	5 yr.	8/28	9/ 1	+	0	0	0	4 7	800 60	90/10 10/90	++ +	79.5 --
12	J2549	M	12 yr.	8/31	9/ 5	++	++	0	++	5 9 18	189 345 33	4/96 8/92 10/90	++ + +0	79.0
13	N1644	M	9 mo.	8/31	9/ 8	+0	0	0	0	9 19	104 60	25/95 10/90	+ +0	57.0
14	N1659	F	1 yr.	9/ 7	9/10	++	++	+	++	3 4	154 200	15/85	+	76.0
15	N1660	M	1 yr.	9/ 6	9/10	+	+	+	+	4 5 17	150 151 51	15/85 5/95 1/99	+0 +0	75.0
16.	N1668	F	1 yr.	9/ 9	9/11	++	++	++	++	2 4 17	35 75 51	8/92 10/90 --	+ + +	105.0
17.	N1669	M	9 yr.	9/ 8	9/11	+	0	0	0	2	82	10/90	+	
18.	N1677	M	13 mo.	9/12	9/13	++	++	0	++	1 14	850 37	40/60 --	0 0	
19.	K1075	F	8 yr.	9/12	9/15	++	0	0	0	3 9	117 21	43/52	+ 0	
20.	N1697	M	6 yr.	9/12	9/15	+	0	0	0	3	150	60/40	0	
21.	J 352	F	8 yr.	9/19	9/20	+	0	0	0	1 2 5	3 4 1	-- -- --		
22.	N1755	M	7 yr.	9/23	9/26	++	0	0	+0	3	185	32/68	+	
23.	N1840	M	4 mo.	10/13	10/15	++	++	0	+	2 3 5	350 170 50	40/60 44/66 10/90	0 0 0	64.0
24.	N1949	F	6 yr.	10/23	10/25	++	0	0	0	3 5	62 15	0/100 15/85	0 0	32.0

*D = No. of days from onset
P/L = Polymorphonuclears/Lymphocytes
C. = City
Co. = County
O. T. = out of town
Adm. = admission

III

CHILDREN'S HOSPITAL DURING THE SUMMER OF 1937

BLOOD SUGAR	C., CO., O. T.	FEVER ° C. ADM.	FEVER ° C. DAYS	RESIDUAL	ADM. W. B. C.	ADM. U. R. T. I.	CONVULSIONS	FUNDI	REMARK
106.0	Co.	40.0	7	s̄	17,300	++	0	+++	Few signs of meningeal irritation, choked disk.
113.0	C.	37.8	19	s̄	9,000	++	0	0	Psychogenic factor.
164.0	Co.	37.5	7	s̄	18,400	+++	+	0	Convulsions on admission.
	C.	40.0	20	c̄	13,000	++	?	0	Epilepsy, psychosis. Mentally defective. Hemiparesis. Death 10/20/37.
	C.	40.0	10	s̄	10,600	0	+	0	Convulsions.
	C.	39.5	10	s̄	20,000	0		0	Tremors of hands—disappeared.
	C.	39.0	5	s̄	4,050	0	+	0	Convulsions, headache, fever, stiff neck.
	C.	39.0	9	s̄	21,250	+	0	0	Headache, fever, Kernig sign, stiff back.
	O. T.	39.0	10	s̄?	13,200	+	0	0	Difficulty in closing jaws, some improvement before discharge.
	C.	40.0	10	s̄	20,700	0+	0	0	Stupor, headache.
136.0	C.	39.5	7	s̄	6,800	+	0	0	Drowsy, fever.
110.5	Co.	40.0	12	c̄	24,200	++	0	0	Drowsy for 13 days. Stare. Psychosis which disappeared.
102.0	C.	39.0	12	s̄	14,400	0	0	0	Stiff back. Drowsy for 9 days.
	Co.	39.0	9	c̄	21,600	++	+	0	Stupor, convulsions. Weak, lt. arm.
109.0	C.	40.0	11	c̄	28,500	0	+	0	Fever, convulsions. Drowsy 4 days. Spastic rt. arm.
148.0	C.	39.0	15	c̄	11,100	++	+	0	Twitching, convulsions. Spastic paralysis of lt. arm and leg. Vacant stare. Mentality (?).
	C.	38.5	6	s̄	11,800	0	0	0	Stiff neck. Fever.
	C.	38.5	9	s̄	32,900	++	+	0	Convulsions, listless 7 days.
	O. T.	38.5	8	s̄	11,700	++	0	0	Headache, fever, stiff neck.
	O. T.	40.0	7	s̄	16,900	0	0	0	Headache, fever, stiff neck.
	C.	40.0	7	s̄	13,600	0	0	0	Stiff neck, fever, headache, drowsy. Opisthotonus.
	C.	39.1	8	s̄	22,000	0	0	0	Stiff neck, drowsy.
89.0	Co.	39.0	7	s̄	20,900	++	+	0	Convulsions, drowsy.
46.0	O. T.	37.5	6	s̄	16,900	+	0	0	Stiff neck, fever. Smallpox vaccination 2 wk. prior to onset.

s̄ = without
c̄ = with

U.R.T.I. = upper respiratory tract infection.

Examination of the cerebrospinal fluid revealed 850 cells with 60 per cent lymphocytes; Pandy test, negative. No organisms were seen or cultured. Convulsions were controlled by chloroform and later amytal.

The temperature continued high for over a week and it returned to normal after two weeks. Baby remained listless for about a week and then gradually he improved, with many fluctuations in his condition. Two weeks after admission the cerebrospinal fluid contained 37 cells and was negative to the Pandy test. The baby was discharged much improved.

CASE 4.—H. G., a 5-year-old boy, had some elevation of temperature and sore throat four days before admission. On the next day he felt better and was up and around.

Two days later he lost his appetite; on next day he became listless; he also vomited once. He complained of headache and generalized aching. The headaches continued the next day, and child became drowsy.

On admission the temperature was 37.5° C. The child was somewhat listless, but rational. The neck was moderately rigid; pharynx was injected. All reflexes were active. There was a suggestion of a Kernig sign.

Lumbar puncture showed an opalescent fluid with 800 cells, 90 per cent polymorphonuclears and 10 per cent Lymphocytes. The Pandy test was positive.

This child was given sulfanilamide the first day.

His condition improved rapidly, and he was in the hospital only three days.

Second lumbar puncture on the day he was discharged showed 60 cells with 90 per cent lymphocytes and 10 per cent polymorphonuclears.

CASE 5.—G. F., a 10-year-old boy, had severe headaches and some abdominal pains four days before admission. His temperature was 101° F., and he vomited several times. The headaches and fever continued. He was rather drowsy and also had one chill. There was some neck rigidity which even increased the next few days. The temperature was 39.6° C. Lumbar puncture yielded a cloudy fluid with a cell count of 200; lymphocytes, 75 per cent; polymorphonuclears, 25 per cent. The Pandy test was 2-plus; spinal fluid sugar, 58 mg. per cent. White blood cells numbered 20,300 and showed a marked shift to the left.

The child was given intravenous glucose repeatedly. The temperature remained elevated for five days after admission. He had also a transient tremor of the tongue and hands. The second lumbar puncture three days later showed 76 cells.

The child's condition improved gradually, and he was discharged after six days in the hospital.

CASE 6.—L. R., male, aged 12 years, "felt bad" four days before entry but had no specific complaints. On next day he had fever and a frontal headache, which persisted until admission.

He vomited on the first two days, but only once or twice a day. His appetite was poor. His temperature rose, and the boy became stuporous.

On admission he was rather drowsy but could be aroused. There was a herpetic eruption about the mouth. The neck was moderately rigid. All reflexes were active. There was a suggestion of a Kernig sign on the left.

A lumbar puncture gave an opalescent fluid with a cell count of 189 cells. The differential count was 96 per cent lymphocytes and 40 per cent polymorphonuclears.

The temperature remained about 40° C. for five days and then gradually subsided.

On the second day the lumbar puncture was repeated. At this time 345 cells were found with 92 per cent lymphocytes.

This boy developed a mild acute psychosis lasting about two weeks. He was given glucose and lactate-Ringer's solution repeatedly, and he had to be fed by gavage.

Finally he improved and was discharged in good condition.

HEMORRHAGIC DISEASE OF THE NEWBORN

A Critical Consideration

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THE term "hemorrhagic disease" was originally suggested by Townsend[1] of the Boston Lying-in Hospital to describe the clinical syndrome of spontaneous bleeding seen in newborn infants. The disease picture has continued to develop as a clinical concept without characteristic pathologic changes, "aside from the hemorrhage and anemia of the tissues."[2] Unfortunately, there are now several definitions of "hemorrhagic disease" differing in important details, with the result that quite dissimilar groups of cases bear the same diagnosis and are made the subject of unjustifiable comparisons. In addition, certain misconceptions are prevalent concerning the mortality to be expected in treated and untreated cases of this disease. Such being the case, it is small wonder that the present literature and statistics concerning this condition are in a state of confusion. A critical review of the subject of hemorrhage in the newborn will be presented in the hope of establishing a common ground from which future studies of "hemorrhagic disease" may depart.

The Relation Between the Definition of Hemorrhagic Disease Employed and the Mortality Encountered

In its original sense "hemorrhagic disease" referred to the syndrome of spontaneous external or internal hemorrhage occurring in the newborn, excluding that associated with trauma, accident, or some definite disease. With the passing of time it was found that infants with "hemorrhagic disease" might or might not show abnormal coagulation or bleeding times. Numerous therapeutic measures, now forgotten, were credited with success in isolated instances. The therapeutic use of whole blood, given subcutaneously or intravenously, was cautiously suggested and became increasingly advocated. While its use was credited with reducing the mortality in this disease, failure to respond to transfusion was not interpreted as of diagnostic significance. It has already been stated that attempts to find a characteristic pathologic picture for this "disease" had failed. It is thus seen that the diagnosis "hemorrhagic disease" was made entirely on a clinical basis, and as such the term was a useful means of classifying an important clinical syndrome of the newborn period.

This is the ninth in a series of studies of the newborn infant death rate. From the Boston Lying-in Hospital, the Departments of Obstetrics and Pediatrics of the Harvard Medical School and the Department of Child Hygiene of the Harvard School of Public Health.

The majority of authors reporting series of cases with "hemorrhagic disease" have fortunately followed this clinical definition. At the Boston Lying-in Hospital this method of classification has been in use since Townsend's time. In applying this definition we do not classify the localized bleeding of traumatic origin in the central nervous system, liver, adrenals, etc., as "hemorrhagic disease." However, if, in addition to the traumatic local bleeding, the infant develops spontaneous external or internal hemorrhages in areas not directly related to the injury, the diagnosis of "hemorrhagic disease" is made. Likewise, macroscopic intracranial hemorrhage occurring in the absence of a history of trauma and associated with multiple hemorrhage in other areas is included in this classification.

That this crude and unscientific classification has proved satisfactory is indicated by the fact that authors following it have been able to report comparable groups of cases (Table I). A tabulation of the cases

TABLE I

An analysis of the reported groups of "hemorrhagic disease" and a recent series of 69 consecutive cases seen at the Boston Lying-in Hospital to demonstrate the incidence of bleeding in the various parts of the body found in each group. The mortality rate for each group is seen to be independent of the type of treatment but directly dependent upon the incidence of bleeding in the vital organs

		INTERNAL AND EXTERNAL BLEEDING							EXTERNAL BLEEDING		
		SCHLOSS & COMMISKEY	CLIFFORD	BEVERIDGE	TOWNSEND	CLARK	DEMBO	JAVERT	CAPON	FALLS	CLIFFORD
Percentage of spontaneous hemorrhage reported in the various organs and tissues	C. N. S.		20	16	10	12	71	7			
	Lungs and pleura		23	24	4			4			
	Skin	30	36	44	42	28		20			30
	Scalp		10	8	4	4					
	Peritoneal cavity		7	8	2						
	Pericardial cavity		14	8							
	Thymus		5	4	2			4			
	Kidney	10	17	4		6		6	2		2
	Adrenal	10	20					3			
	Liver	10	9					1			
	Umbilicus	30	10	28	36	24	2	10	+	5	7
	G. I. tract	60	82	100	80	62	27	64	92	100	94
	Vagina		12					8	3		10
Total number of cases		10	69	24	18	50	55	72	61	14	40
Incidence rate			1-333		1-204	1-118		1-157	1-405		1-506
% given I. M. or S. C. Whole Blood		100	4	0	0	88	35	72	50	0	0
% given I. V. Whole Blood Transfusions		0	84	8	0	4	13	70	13	100	95
Mortality per cent		30	30	33	33	38	53	16	8	0	0

reported under this classification by Townsend,[1] Schloss and Commiskey,[3] Beveridge,[4] Clark[5] and of the 69 cases I have just reviewed from this hospital shows the incidence of bleeding in the various organs and tissues to be surprisingly uniform from group to group. Furthermore, the mortality encountered was consistently between 30 and 38 per cent, while the incidence rate was between 1-118 and 1-333 births.

As soon as an author alters the proportion of the various types of cases admitted to his group by changing the definition of "hemorrhagic disease" or otherwise selecting cases, his results must be interpreted with reservations and not compared with groups of dissimilar composition (Table I.) In spite of the obviousness of this point much of the present confusion surrounding "hemorrhagic disease" can be traced to such comparisons between incomparable groups.

Von Reuss[6] gives Townsend's figure of 79 per cent as the mortality of melena vera, and on this authority the figure has been widely quoted. Von Reuss realized, however, that "the cases probably are not limited to melena vera in the strict sense of the term," but this qualifying statement has not been mentioned in subsequent references. We have already seen that Townsend's group included other types of bleeding (Table I) than melena vera. Yet from this began the legend that untreated melena vera carried a 79 per cent mortality. We will return to consider Townsend's supposed 79 per cent mortality later in this paper.

Capon[7] decided that the diagnosis of "hemorrhagic disease" should be reserved for cases of external bleeding such as melena vera, hematemesis, hematuria, and umbilical, mucous membrane and vaginal bleeding. He excluded cases with internal bleeding in the adrenals, peritoneal cavity, liver, and intracranial cavity as being generally of traumatic origin. By this process of exclusion Capon[8] was able to quote a mortality of 8 per cent for his series of 61 cases. In the 69 cases of "hemorrhagic disease" from the Boston Lying-in Hospital the mortality was 30 per cent; but, if Capon's diagnostic criteria are applied, 29 of the cases must be excluded. In the 40 remaining cases of "hemorrhagic disease," by Capon's standards, the mortality was zero (Table I). Of the 29 excluded cases, there were 20 deaths or a mortality of 70 per cent. When Capon makes the statement that "the death rate is now definitely lower than it was before the introduction of blood treatment," one has a right to question whether the lowered death rate was not the result of a redefinition of the disease that automatically excluded the serious cases.

Dembo[9] has reported a series of 55 cases of "hemorrhage in the newborn." In his group are reported 16 cases of "hemorrhagic disease" with gastrointestinal and umbilical bleeding and 39 cases of intracranial hemorrhage. His cases with intracranial hemorrhage are of two types, one accompanied by general oozing from the mucous surfaces, particularly the gastrointestinal tract—this type we would include in

the diagnosis of "hemorrhagic disease." The second type "includes hemorrhage involving the brain and meninges resulting largely from traumatism"—this type we would not include in the classification. While Dembo properly titled his series as hemorrhage in the newborn and not "hemorrhagic disease," he compared his 53 per cent mortality on the one hand with those of the Townsend (62 per cent mortality, q. v.) and Beveridge (33 per cent mortality) groups of clinical "hemorrhagic disease" and on the other with the Robertson, Brown and Simpson*[10] (2.3 per cent mortality) and Falls[11] (0 per cent mortality) groups of melena vera. Since 13 per cent of Dembo's patients (53 per cent mortality); none of Townsend's patients (62 per cent mortality) and 8 per cent of Beveridge's patients (33 per cent mortality) were transfused, while in contrast all of Robertson, Brown and Simpson's patients (2.3 per cent mortality) and all of Falls' patients (0 per cent mortality) were transfused; Dembo concludes that "a comparison shows rather definitely the importance of blood therapy." The fallacy in the above argument should require no comment.

There is a more convincing explanation available for the high mortality encountered in Dembo's cases. Between my own series of 69 cases with 30 per cent mortality and Dembo's with 53 per cent, there is one important difference: I did not include cases of traumatic intracranial hemorrhage unaccompanied by spontaneous bleeding elsewhere, under the diagnosis of "hemorrhagic disease." As a result, 20 per cent of my cases showed macroscopic intracranial hemorrhage, whereas 71 per cent of Dembo's cases had this finding. The inclusion of large numbers of traumatic intracranial hemorrhage cases in Dembo's series adequately explains his higher mortality—transfusion or no transfusion.

In summary, the broad definition of "hemorrhagic disease" given in the second paragraph of this paper results in comparable groups of cases having a mortality rate between 30 and 38 per cent. By changing the above definition of "hemorrhagic disease," the mortality can be manipulated either up or down to practically zero. The lowered mortality resulting from reclassification naturally should not be credited to any therapeutic procedure. The higher mortality resulting from the inclusion of a large number of cases of internal hemorrhage similarly should not be charged as therapeutic failure or explained as the result of the failure to use whole blood in treatment.

THE INFLUENCE OF METHOD OF TREATMENT ON MORTALITY IN HEMORRHAGIC DISEASE

Practically every article written on "hemorrhagic disease" quotes Townsend's figures as the mortality to be expected in untreated cases of

*That this group is composed of the external bleeding type of case is an assumption on my part. The authors do not state their definition of "hemorrhagic disease." They do state that "all cases of hemorrhage of the newborn were cured, save one which succumbed to extensive cerebral hemorrhage." The one case history presented was of umbilical hemorrhage.

the disease. Holt and McIntosh[2] state, "Before the introduction of treatment with whole blood, the prognosis was very bad; of 709 cases collected by Townsend the mortality was 79 per cent. Now with proper treatment most cases recover." A review of Townsend's papers reveals that his mortality in "hemorrhagic disease," as the term is now understood, was actually 33 per cent—practically the same figure as those since reported by various authors in comparable groups of cases irrespective of the treatment employed.

Townsend's first paper,[12] published under the title of "Hemorrhages in the New Born," consisted of a series of 32 cases encountered in 7,225 deliveries at the Boston Lying-in Hospital. In this group there were 25 deaths, or a mortality of 79 per cent. By reference to the hospital records these deliveries overlapped the period of the introduction of the "aseptic technique" during which the neonatal mortality rate was falling from 79 to 36 per 1,000 births.

Townsend's second paper,[1] in which he introduced the term "hemorrhagic disease," presented 18 additional cases occurring in 3,575 deliveries. In this group there were 6 deaths, or a mortality of 33 per cent. During this period, from 1891 to 1894, the hospital neonatal mortality rate was 25 per 1,000 births. The literature has quoted Townsend's mortality as either the 79 per cent of the first series or the 62 per cent of the combined series. For some reason the mortality of the second series has never been mentioned, even by Townsend. The mortality of 33 per cent for the second series of untreated cases would seem to be the one most comparable to present conditions.

Table II summarizes the effects of various types of blood therapy on the mortality in comparable groups of "hemorrhagic disease."

TABLE II

AUTHOR	NUMBER OF CASES	% TREATED BY I. M. OR S. C. BLOOD	% TREATED BY BLOOD TRANSFUSION	MORTALITY %
Townsend	18	0	0	33
Beveridge	24	0	8	33
Schloss and Commiskey	10	100	0	30
Clark	50	4	88	38
Clifford	69	4	84	30

The rationale of treating "hemorrhagic disease" with whole blood has been based on the assumption that the expected mortality in untreated cases is 79 or 62 per cent, while "now, with proper treatment most cases recover."[2] The above assumption is open to question, for the mortality in untreated cases is found to be 33 per cent; in inadequately treated cases it is 33 and 30 per cent, while in adequately treated cases the mortality is still between 30 and 38 per cent. Furthermore the low mortality rates reported in the literature have not been in groups of "hemor-

rhagic disease'' as defined above, but in cases of melena vera, hematemesis, etc., where a favorable mortality rate may be anticipated—treatment or no treatment.

Several authors have already expressed doubts as to the efficacy of certain types of whole blood therapy in the milder forms of the disease. Capon[8] states that ''cases of average severity seem to respond satisfactorily to the intramuscular injection of human blood, but, having admitted that the disease tends to be self-limited, it is obviously difficult to decide whether special treatment has played any definite part in recovery.'' Sanford and Leslie[13] venture the opinion that ''we do believe that children who recover following small injections of whole blood intramuscularly would recover spontaneously.''

They go a step further and say, ''The procedure of injecting small quantities of parents' blood intramuscularly into newborn infants as a prophylactic measure is not only needless, but in some cases might actually increase the coagulation time of the blood.''

There is no difference of opinion as to the value of whole blood transfusion in combating the anemia accompanying severe hemorrhage in the newborn, whatever its cause. Under these circumstances its effect is often dramatic and life saving. Whether blood therapy has any other place in the treatment of ''hemorrhagic disease'' is a proper subject for future investigation.

THE RELATION OF ABNORMAL BLEEDING OR COAGULATION TIMES TO HEMORRHAGIC DISEASE

The remaining source of confusion concerns the relation of abnormal bleeding or coagulation times to ''hemorrhagic disease.'' Schloss and Commiskey,[3] Javert,[14] and the writer have all encountered abnormal coagulation or bleeding times in considerably less than one-half of the cases of ''hemorrhagic disease.'' As Schloss and Commiskey[3] state, ''absence or delay of the onset of coagulation is not constant in hemorrhagic conditions of the newborn.''

In contrast with these views Rodda[15] contends that ''the cause of hemorrhagic disease of the newborn is some physical or chemical change in the blood which produces delay and impairment in coagulation properties. The most constant finding in this disease is a delayed coagulation and protracted bleeding time. These findings may antedate any symptoms by hours or even days. These changes may be the only sign of hemorrhage, external bleeding failing in many cases.'' Sanford and Leslie[13] have applied Rodda's ideas in a most literal manner and have demanded a prolongation of coagulation time before true ''hemorrhagic disease'' can be diagnosed. In eight years and in 5,500 births only 2 infants were found suffering from the ''true'' disease. Coppolino[16] was even more exacting and demanded a prolongation of both bleeding and coagulation

time. On this basis he could find but one case of "true hemorrhagic disease" in every 1,548 births. His comment is significant, "Although we have observed many hemmorhages of the newborn, nevertheless, we have noted only 2 cases which could be called hemorrhagic disease."

That "hemorrhagic disease" is the result of some primary blood dyscrasia, evidenced by an abnormality in the bleeding time or coagulation time or by an alteration in the prothrombin level, is an important field for investigation. Studies on this aspect of the problem are going on in many clinics, but as yet there is no agreement as to the etiology of "hemorrhagic disease."

Others have not been able to attach as much importance to coagulation and bleeding times as have Rodda and his followers. Sanford and Leslie and Coppolino demonstrated that to require an abnormal coagulation time or bleeding time or both before the diagnosis is made would make "hemorrhagic disease" a rare condition of no practical importance and leave no means of classifying the many cases of hemorrhage of the newborn unaccompanied by blood changes.

In the present state of our knowledge it would be unwise to attempt an etiologic classification of "hemorrhagic disease."

CONCLUSION

The diagnosis of "hemorrhagic disease" can be made only on clinical grounds until its etiology is established, in the absence of characteristic pathologic or consistent laboratory findings. "Hemorrhagic disease" is a loose clinical syndrome and not a true disease entity.

Premature efforts to redefine "hemorrhagic disease" on an etiologic basis have only resulted in confusion and should be abandoned. Abnormal coagulation or bleeding times should not be a prerequisite for the diagnosis. Cases with internal hemorrhage should not be automatically excluded as presumably of traumatic etiology.

The most important factors influencing the mortality in "hemorrhagic disease" are the points of origin of the bleeding. Cases with external hemorrhage alone not only are most frequently encountered but have practically no mortality. Cases with internal or internal and external hemorrhage have a mortality of 70 per cent at the Boston Lying-in Hospital.

The subdivision of cases of "hemorrhagic disease" into groups according to the location of bleeding is desirable, but obviously the resultant group is no longer comparable to the original one. The impression that the present mortality in "hemorrhagic disease" is very low has grown out of such unjustified comparisons.

In comparable groups there has been no appreciable mortality reduction in "hemorrhagic disease" from 1894 to the present, irrespective of the type of treatment or lack of treatment.

In the treatment of severe anemia, irrespective of its cause, transfusion with whole blood is of tremendous value and frequently is life saving.

There is need for further investigation of "hemorrhagic disease," particularly the type with internal bleeding, with a view toward establishing its etiology, treatment, and prevention.

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BACTERIUM ALKALESCENS IN THE STOOLS OF NORMAL INFANTS

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SERIAL studies of the fecal flora of twenty-three normal infants showed three babies to have consistently large numbers of dysentery organisms in their stools. These strains were at first identified as *Bact. dysenteriae* (Flexner), but later studies showed them to be *Bact. alkalescens,* a species closely related to the Flexner type but to which Andrewes[1] ascribed doubtful pathogenicity.

Following Shiga's description in 1898 of the organism associated with an epidemic of dysentery in Japan,[2] several types of dysentery bacilli were isolated and classified in a short time. Their relation to the summer diarrhea of infants was quickly sought, and extensive investigations were made. The failure to recover these or similar forms from the stools of normal infants was recorded by Wollstein,[3] Davison,[4] and Soule and Heyman,[5] but Duval[6] stated that he found the Flexner type in the stools of normal bottle-fed infants. Collins[7] also obtained *"Bacillus paradysenteriae"* in one of a series of ten normal infants, a 2-year-old child who had no previous history of diarrhea. However, she could not find any of these organisms in a duplicate series. The presence of dysentery bacilli in the stools of infants led Veeder, Kilduffe, and Denny[8] in 1912 to the conclusion that the appearance of a few dysentery bacilli was of little significance and even in a case of colitis did not mean that these germs were the cause of this condition.

Specifically, the presence of *Bact. alkalescens* in the stools of normal infants has not, as far as the author is aware, been reported. Its occurrence has for the most part been associated with abnormal conditions of the urinary tract as recorded by Weil,[9] Popoff and Spanswick,[10] Smith and Fraser,[11] Welch and Mickle,[12] Murray and Pike,[13] Starkey,[14] Mackenzie and Ratner,[15] Snyder and Hanner,[16] and Neter.[17-19] In these instances *Bact. alkalescens* was usually isolated from the feces. However, its presence in the blood stream was observed by Smith and Fraser as well as by Starkey. Welch and Mickle found *Bact. alkalescens* in the stools of several university students during an acute outbreak of dysentery which could be traced to a food handler who was a carrier. Neter also mentioned the isolation of *Bact. alkalescens* from the stool of a healthy person.

Because of these references dealing with the presence of *Bact. alkalescens* in normal and pathologic intestinal and urinary tracts, it seemed of interest to report the following observations.

This work was done as Child Research Fellow in the Department of Bacteriology and Public Health and Child Research Council, University of Colorado School of Medicine, Denver.

MATERIAL

This study of *Bact. alkalescens* represents only a small portion of the work done on the feces of twenty-three infants under 1 year of age who were a part of a group of one hundred children being followed from birth to adolescence by the staff of the Child Research Council. In addition to the extensive routine quarterly examination given these children, stools were obtained biweekly from the breast-fed infants and monthly from the babies who were weaned. With the exception of one baby there was no acute gastroenteritis recorded. All of the infants were normal in development as determined by exhaustive clinical study.

The isolation of a dysentery bacillus in the one case of gastroenteritis cast suspicion upon it as the etiological agent. However, similar organisms were also found in the stools of two normal infants. No other apparently abnormal species was observed. Brief histories of the three babies are as follows:

CASE 1.—A baby girl, 6 weeks old at the time of the first examination, had recently been transported from Idaho to Denver, and after her arrival started to pass six to eight watery greenish stools a day which contained mucus but no blood. Recovery without medication was complete within a fortnight. No more trouble was recorded during the period of observation, which was up to 1 year of age. Although the baby was breast fed, there was the possibility of infection by water during the journey.

CASE 2.—A male child, 6 months old and already weaned before his first examination, had no previous record of diarrhea or dysentery. During the next six months there was likewise no occurrence of gastrointestinal trouble.

CASE 3.—The first stool was obtained from this healthy breast-fed male infant when he was 4 weeks old. Except for a slight diarrhea at 5½ months when the first teeth erupted, no abnormal intestinal condition was noted.

The stools of the breast-fed infants were characteristically deep yellow in color, semisolid in texture, and acid in reaction. After weaning, the usual shift to the darker stools with fecal odor was observed. Microscopically, slide smears of the nurslings' feces were observed to be almost uniformly composed of slender or slightly curved gram-positive rods, some of which showed bifid forms. These organisms were assumed to be *Lactobacillus bifidus.*

To obtain members of the colon-typhoid-dysentery group, suspensions of the specimens were made in normal saline of which a loopful was streaked over the surface of an eosin-methylene-blue agar plate. Instead of the ordinarily expected metallic colonies of *Bact. coli* or the mucoid growth of *Bact. aerogenes,* it was extremely interesting to find numerous smooth flat grey or white colonies which even replaced the coliform organisms, as in Case 3 when it was the fourth month before *Bact. coli* appeared. These organisms were repeatedly isolated in Cases 1 and 3 up to 6 months of age, after which they appeared less frequently. For the

other members of the fecal flora in these babies the author's thesis[20] may be consulted. To show the regularity of the presence of *Bact. alkalescens* the results of the periodic examinations are given in Table I.

TABLE I

FREQUENCY OF ISOLATION OF *Bact. Alkalescens* IN THE FECES OF THREE BABIES UNDER ONE YEAR OF AGE

CASE	WEEKS																	
	4	6	8	10	12	14	16	17	18	19	22	24	28	32	36	40	44	48
1 (7204)*		+	+	+	+	+	+	+		+	+	+	0	0	0	+	0	0
2 (7166)												+	+	+	0	0	0	0
3 (7404)	+	+	+	+	+	+	+		+		+	+	0	+	+		0	+

*Serial numbers for laboratory cultures of hospital material.

LABORATORY STUDIES

Preliminary work showed these suspicious forms on eosin-methylene-blue agar to be short nonmotile rods that did not ferment lactose or liquefy gelatin. Fermentation of mannite tentatively classified the groups as strains of *Bact. dysenteriae* (Flexner). However, extended cultural studies revealed the constant production of acid in dulcitol which identified the strains as *Bact. alkalescens* (Andrewes[1] and Bergey[21]). Acid was not produced in lactose in two weeks, which reaction differentiated these strains from the mutating Sonne and Dispar types. The cultural reactions were repeated at the Hygienic Laboratory and compared with two strains of *Bact. alkalescens* sent by Professor E. D. G. Murray, of McGill University, one of which was the urinary strain (49226) isolated by Starkey and the other a subculture of Andrewes, original *Bact. alkalescens.* The urinary strain (7172) of Snyder and Hanner was also included. The cultural reactions of these strains and *Bact. dysenteriae* (Flexner) are given in Table II.

TABLE II

CULTURAL REACTIONS OF STRAINS OF *Bact. Alkalescens* COMPARED WITH *Bact. Dysenteriae* (FLEXNER)

	GLUCOSE	LEVULOSE	GALACTOSE	MALTOSE	LACTOSE	SUCROSE	XYLOSE	SALICIN	MANNITOL	DULCITOL	GLYCERIN	GELATIN	INDOL	LITMUS MILK
Case 1 (7204)	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
Case 2 (7166)	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
Case 3 (7404)	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
7172	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
49226	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
Bact. alkalescens	A	A	A	A	O	O	A	O	A	A	O	O	+	Alk.
Bact. dysenteriae (Flexner)	A	A	A	A	O	O	O	O	A	O	O	O	+	Alk.

Table II shows the uniform fermentation with acid but no gas of glucose, levulose, galactose, maltose, xylose, mannitol, and dulcitol by the

strains of *Bact. alkalescens*, whereas *Bact. dysenteriae* (Flexner) did not produce acid in xylose or dulcitol. The reactions with mannitol and dulcitol are in accord with the excellent differential chart given by Andrewes and Inman.[22] Milk was also turned alkaline more rapidly with the *Bact. alkalescens* than with the Flexner type.

Another characteristic of *Bact. alkalescens* as pointed out by Andrewes is its susceptibility to agglutination by acid after the method of Michaelis.[23] This feature is in contrast to the inagglutinability of dysentery bacilli by these acid concentrations (Michaelis[24]). All the present strains of *Bact. alkalescens* could be shown to be completely flocculated in buffers of pH 3.2-2.4. The Flexner strain was not agglutinated by respective hydrogen ion concentrations.

Serologically, Andrewes found *Bact. alkalescens* to stimulate antibody formation with difficulty. In his monograph with Inman, however, he noted that good agglutination could be obtained by incubation at 55° C. for twenty to twenty-four hours. He felt that this delayed reaction by *Bact. alkalescens* and lactose fermenters *(B. ambiguus)* was so striking as to be regarded of special significance. Also, a common antigen with the Flexner type, especially at 55° C., was present. Weil, Smith and Fraser, Popoff and Spanswick, Welch and Mickle, and Neter were likewise able to obtain not only specific antibodies but also showed a common antigen with Flexner which could be absorbed. Preliminary tests with the strains at time of isolation showed 7204 and 7404 to agglutinate with a known Flexner antiserum but not with Shiga, Park, Hiss Y, and Sonne antisera. Strain 7166 was not agglutinated by the Flexner antiserum. The reactions of these strains with an antiserum prepared against Strain 7404 are listed in Table III.

TABLE III

CROSS-AGGLUTINATION TESTS OF STRAINS OF *Bact. Alkalescens* ISOLATED FROM INFANTS WITH AN ANTISERUM PREPARED AGAINST ONE OF THE FECAL STRAINS, 7404

	SERUM DILUTIONS									
	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120	Cont.
7204	–	–	–	–	–	–	–	–	–	–
7166	–	–	–	–	–	–	–	–	–	–
7404 (hom.)	++++	++++	++++	++++	++++	++++	++++	++++	++++	–
Flexner	++++	++++	++++	++++	++++	++++	++	–	–	–

Here again the relation of Strain 7404 to the Flexner type is shown, but there was no macroscopic agglutination with the other two strains.

After these tests the cultures were placed on agar slants and sealed for more than a year, when they were opened for additional study. Routine transfers were made from one- to three-month intervals. All strains when first plated on nutrient agar showed the colonies to be mostly smooth with some colonies showing slightly wrinkled edges in forty-eight

to seventy-two hours. Recently the Andrewes and 7166, 7404, 49226 strains were found to be completely dissociated into the R colony form.

Preparation of antisera against the Flexner type and Strains 7172, 7204, 7166, and 7404 was done with heat-killed saline suspensions as antigens which were given subcutaneously in rabbits in 2.0 c.c. doses ten times at four-day intervals, and the rabbits were bled for serum a few days after the last injection. Macroscopic tests showed no agglutination of the strains of *Bact. alkalescens* by the Flexner antiserum. Strain 7172 was not flocculated by its own or the other antisera, but the Andrewes, 7166, 7204, and 7404 strains and the Flexner type agglutinated up to a 1:40 serum dilution, and occasionally partial clumping as high as 1:320 by antisera 7204, 7166, and 7404 was observed. Antisera prepared against the Andrewes and 49226 strains showed a similar lack of agglutinins. The tests on the whole were very inconclusive.

Since plain broth cultures flocculated somewhat better than saline suspensions, new rabbits were inoculated with forty-eight-hour broth cultures of the Andrewes and 7204, 7172, 7166, 7404 strains, which were given either subcutaneously (2 c.c.) at four-day intervals or three weekly series of daily intravenous doses (0.5 to 2 c.c.) with a week's interval between the series. The agglutination reactions with these new antisera were not significantly different from the preceding ones.

Failing satisfactory agglutination tests, recourse was made to the complement fixation test as recommended by Starkey. Portions of 7204, 7172, Andrewes and Flexner antisera were heated to 56° C. for thirty minutes and mixed with saline suspensions diluted to a point determined not to be anticomplementary. In the presence of complement and a hemolytic system the results are recorded in Table IV for a 1:20 serum dilution.

TABLE IV

COMPLEMENT FIXATION TESTS WITH *Bacterium alkalescens*

BACTERIAL SYSTEM: ANTIGEN 0.2 C.C. SALINE SUSPENSION
SERUM 0.2 C.C. (1-20)
COMPLEMENT 0.2 C.C. (1-20)
HEMOLYTIC SYSTEM: AMBOCEPTOR 0.2 C.C. (1-200)
R.B.C. (SHEEP) 0.5 C.C. 2 PER CENT SUSPENSION
INCUBATION: BACTERIAL SYSTEM INCUBATED IN A WATER BATH 30 MINUTES AT 37°. HEMOLYTIC SYSTEM ADDED AND INCUBATED FOR AN ADDITIONAL 30 MINUTES

	7172	7166	7204	7404	49226	*Bact. alkalescens*	FLEXNER	CONTROL—NO COMPLEMENT	CONTROL—NO ORGANISMS	CONTROL—NO ANTISERUM	HEMOLYTIC SYSTEM
7172	O	O	O	O	O	O	C	O	C	C	C
7204	O	O	O	O	O	O	C	O	C	C	C
Bact. alkalescens	O	O	O	O	O	O	C	O	C	C	C
Bact. dysenteriae (Flexner)	C	C	C	C	C	C	O	O	C	C	C

C = Complete hemolysis.
O = No hemolysis.

Serum dilutions of 1:5 and 1:10 gave the same results; namely, that there were apparently specific antibodies produced by the *Bact. alkalescens* strains which did not fix complement in the presence of Flexner antigen.

DISCUSSION

The interesting feature in this study was the isolation of *Bact. alkalescens*, a dysentery bacillus, from the stools of three normal infants in only one of whom occurred a marked gastroenteritis. In this instance it seemed probable that these organisms were the cause of the illness, since there were no other pathogenic forms demonstrated. Their presence was not chance finding since they were repeatedly obtained and in one case were the only gram-negative aerobic nonsporulating rods in the stools up to the fourth month, when a few coliform bacteria appeared. Except for the possibility in Case 3 in which a similar organism was found in the father's stool, the source of infection could not be determined. These findings support the slight pathogenicity of *Bact. alkalescens* as reported in the literature. However, the chance of increased virulence through transmission remains, and thus a public health problem is raised.

On a cultural basis the fermentation of dulcite seems to be the chief differential criterion and for routine diagnostic purposes should serve to separate *Bact. alkalescens* from the Flexner, Hiss Y, Park, and Strong varieties. Serologically, however, the problem is complicated by the inability of some strains either to stimulate the production of antibodies or to agglutinate with known serum. Neter (personal communication) thinks there are three types of agglutination response with this species: first, a high titer agglutination; second, a delayed though high titer agglutination; and third, sera with little or no ability to agglutinate. A high titer serum (2567) prepared by Neter failed to agglutinate any of the present *Bact. alkalescens* strains, but it did agglutinate the Flexner strain to a serum dilution of 1:1280, and its homologous antigen 1:5,120. Complement fixation tests with this serum showed Neisser-Wechsburg types of antigen-antibody combination with the Andrewes and 7404 strains in serum dilutions of 1:80 and 1:160 but not at 1:20 and 1:40. Strains 7166, 7172, 49226, and 7404 did not fix complement, but the Flexner strain absorbed the complement in a serum dilution of 1:160.

Recent observations on these strains showed all but 7204 to be completely or nearly completely dissociated into the rough phase on the basis of colony morphology. The Flexner type remained smooth. Undoubtedly this change explains some of the difficulties and divergent results encountered in the serological tests, but considering the inability to produce antibodies even with freshly isolated smooth strains, it would appear that bacterial variation was not the whole story. In an exchange of strains and antisera of *Bact. alkalescens* with Dr. Neter, both of us obtained little or no agglutination with the present strains as antigens and his high titer *Bact. alkalescens* (2567) antiserum as the antibody. However,

Neter pointed out, as Andrewes had already indicated, that extensive agglutination took place at 55° C. in forty-eight hours with all strains except 7172. This delayed reaction could be confirmed. Further studies are being made to determine other variables besides temperature acting upon the antigen-antibody reactions of *Bact. alkalescens*. At present it would seem that while strains of *Bact. alkalescens* exist that are capable of producing high titer antisera, the strains under study do not possess this power. As a result of low and irregular agglutination response, no absorption tests were made; only the gross relationship of the strains of *Bact. alkalescens* to each other and the Flexner type was indicated.

SUMMARY

Strains of dysentery bacilli were frequently isolated from the stools of three infants under one year of age. Only one of these babies had any history of gastrointestinal trouble. The identity of these organisms with a subculture of the original strain of *Bact. alkalescens* was shown by cultural tests. The serologic picture was complicated by the inability of the strains to stimulate the production of agglutinins or other antibodies so that adequate titers for absorption tests could be made. Nevertheless, the strains seemed to have an antigen in common which was also shared by the Flexner type in the agglutination test but not in the complement fixation reaction.

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PHENYLKETONURIA AND THE CONGENITALLY DEAF

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IN 1934 Følling[1] recorded the presence of phenylpyruvic acid in the urine of ten aments, and in 1935 Penrose[2] recorded two cases in aments. No history of deafness is recorded in any of these cases. A. F. Tredgold[3] made an investigation of five of these cases and could not discover any special characteristics that would distinguish them from typical primary aments. To check on this test Tredgold, with the aid of Dr. Maizels of University College Hospital and Dr. Golla of Mandsley Hospital, each checked 200 normal patients, both series of which were negative.

Penrose concludes that phenylketonuria is due to a single recessive gene and that it does not appear in the nondefective relatives of the affected individuals. Tredgold believes that this error in metabolism is not the cause of the mental defect but merely another example of the well-known fact that defects of mind are usually accompanied by defects of body.

The technique of the test is simple.

1. Be sure the urine specimen is acid in reaction.
2. Add 5 to 10 drops of 5 per cent ferric chloride to the acidulated specimen.

A positive test is recorded if a dark green color appears.

I thought it would be interesting and also add to the value of the test if the results at the Ohio State School for the Deaf were reported. Specimens from 320 pupils were tested for phenylpyruvic acid.

The cause of deafness in approximately half of these children is hereditary defects of the middle ear or auditory nerve. In no case was phenylpyruvic acid demonstrated.

I believe it can be definitely stated that hereditary types of deafness are not accompanied by phenylketonuria.

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COOLEY'S ANEMIA (MEDITERRANEAN ANEMIA)

With a Report of a Case in an Adolescent

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COOLEY'S anemia (erythroblastic or Mediterranean anemia) is so rarely encountered in subjects past childhood that we have been able to uncover only six reported cases. We now add one in the adolescent period, the case of a girl, 14 years of age, who presents all the striking characteristics of this disease.

REVIEW OF THE LITERATURE

In 1889 and 1890, under the title of "pseudo-leukemia infantum," von Jaksch first described a series of cases of anemia, with leucocytosis and enlarged spleen and liver. The disease occurred in infancy or childhood and tended to recover. "Pseudo-leukemia infantum," later to be known as von Jaksch's anemia, became a category into which many of the ill-defined anemias of childhood were grouped. There were no definite limits to this classification. Different conditions such as rickets, syphilis, malaria, hemolytic icterus, and the aleucemic stage of leucemia were grouped under this one heading.

Stillman and Pool[15] were among the first to realize that within this classification of von Jaksch's anemia there was a disease entity with definable characteristics, of which moderate enlargement of the liver and great enlargement of the spleen were prominent features. The prognosis was not favorable.

Stillman's case M.M. is of particular interest.[14] One cannot read her case history, operative report, and subsequent history without realizing that this case with its erythroblastic crisis subsequent to splenectomy, represents a true deviation from what was being described as von Jaksch's anemia. It is noteworthy that Stillman insisted these patients did better after splenectomy.

In 1925 Cooley and Lee[9] reported five cases of von Jaksch's anemia which to them represented a group distinctly apart from what had hitherto been described under the same term. Emphasis in this report was placed on the nucleated red blood cells (especially after splenectomy), the facies, and the large abdomen due to the tremendous spleen. Three of their patients died, one had syphilis, and one was living after splenectomy. Cooley and his co-workers,[6, 10] by their reports in 1927, brought the medical world to realize that the anemia they described in

From the Newcomb Hospital.

definite terms could be separated from the group of indefinite splenic anemias. They questioned the use of the term von Jaksch's anemia since it was ambiguous and tended to cloud the picture by suggesting that it was associated with a favorable outcome. In 1928 Cooley[7] pointed out that there were certain characteristics in the anemia he described that might prompt linking this disease with hemolytic anemia and sickle-cell anemia, but he was careful also to contrast the differences.

Baty, Blackfan, and Diamond[2] reviewed along with their own cases several cases of the disease already reported. Theirs is a classical report of the disease. An analysis of their statistics showed that when the condition was diagnosed in the first year, life extended about 16 months. The life expectancy in their series was 45 months when the condition was diagnosed in children over one year of age. Their comment was that these children rarely grew to adulthood. They quote Dr. F. W. Peabody in saying that the bone marrow of Cooley's anemia resembles that of pernicious anemia in the stage of relapse, but they carefully point out that here the similarity of the two diseases ends.

Whipple and Bradford[16] wrote of the disease as one in which there was a fundamental disturbance of bone and pigment metabolism. Whipple, in autopsy reports, described abnormal pigment deposits in the salivary glands, mucous glands (mouth and bronchi), Brunner's glands, the ductless glands, liver, and spleen. In a later article Whipple and Bradford[17] state "that the pigment deposits are just as characteristic of this disease complex as are any other factors." They discuss the bone changes as due to the lack of a vital factor in metabolism and question whether this is a vitamin or a glandular element. They compare this lack of a vital factor to that of pernicious anemia and are careful to point out that it is not the same factor.

Cooley, Witwer, and Lee[10] disagree with Whipple and Bradford as to the causation of the bone hyperplasia. The first group ascribes the hyperplasia to the overstimulation of an inefficient bone marrow to supply the needs of the body; the cortex of the bone then becomes thin, being insufficiently developed to withstand the hyperplasia of the marrow.

Various authors have described different causes of the disease. As recently as 1937, Nittis and Spilopulos[13] presented a series of cases said to have been caused by malaria. They treated their series with quinine and claimed to have obtained cures. Dr. I. J. Wolman (personal communication of work not published) of the Children's Hospital of Philadelphia has not been able to duplicate successfully this work in a series of cases under his care.

Bennett, Hunter, and Vaughan[3] report a case of an adult with severe anemia, erythroblastosis, osteoporosis, and secondary anemia as well as thickening of the bones of the skull. Their case is amply explained on the basis of the severe secondary anemia and deficient calcium absorp-

tion of celiac disease. This and other cases weaken the theory that celiac disease is a cause of the blood and bone changes of Cooley's anemia.

The reports in the literature concern children of Greek and Italian parentage, with one exception—a child of Irish-English parentage reported by A. J. Grinnan.[11] This may well have been a case of hemolytic anemia because of his statement: "At the end of one year and three months no erythroblasts were found in the blood smear, and the red count and hemoglobin showed a fairly marked improvement." Unfortunately, too, no x-ray reproductions were included in the paper.

Caffey,[4] in reporting a series of 21 cases of Cooley's anemia, observes that there are cases that show the long bone changes yet lack the characteristic radiative thickening of the skull. He says: "After following these mild cases over several years, it seems certain that such patients reach adult life and probably old age, and that mild erythroblastic anemia is not limited to infancy and childhood. This suggests that such mild adult cases might transmit the disease to their offspring. However, we have never found the slightest evidence of erythroblastic anemia, either clinical, hematologic, or roentgenologic, in the parents of our erythroblastic infants and children." We quote this because it seems prophetic to us.

Caminopetros (1938)[5] has reported 36 cases of Cooley's anemia, two of which were in adults. He believes malarial therapy is best suited to arrest the excessive activity of the hematopoietic system. How contrary to Nittis and Spilopulos, who believed quinine therapy indicated! Benjamin Kramer (in a personal communication from the Jewish Hospital of Brooklyn) studied a case of Cooley's anemia in a patient who was 11 years old in 1933. This patient died at 16 years of age. She was of Italian extraction and had all the classical symptoms of the disease.

The five cases of Cooley's anemia thus reported in the literature and one case by personal communication from Kramer in patients over 14 years of age are (1) Stillman's case,[14] reported by Cooley[8] as being over 25 years of age in 1932; (2) a patient 15 years old reported by Mandeville in 1930[12]; (3) a male 24 years old reported by Allen and Childs[1] in 1936; (4) and (5) two adults reported by Caminopetros[5]; and (6) a 16-year-old female (personal communication from Dr. Kramer).

CASE HISTORY

L. L. was born March 14, 1924, a normal full-term child who is said to have weighed 9 pounds at birth. She was breast fed until the ninth month and had cereals from the sixth month. Orange juice was administered throughout infancy, but no cod liver oil was given. She walked at about the tenth month and talked at one year of age.

The mother dates the onset of the child's illness to about the tenth month, when she noticed that the child no longer gained in weight and became increasingly pale. She did not appear weak. Toward the end of the second year, the family thought

it advisable to send her to relatives in the country so that she would improve in health. In 1929 she was admitted to the Jewish Hospital of Philadelphia under the care of Dr. Harry Lowenberg.* At that time a diagnosis of von Jaksch's anemia was made. A spleen about five times larger than normal was removed.

From 1929 to 1937 she had been repeatedly admitted to the Mount Sinai Hospital of Philadelphia (service of Dr. Lowenberg), with the diagnosis of Cooley's anemia. Several of these admissions were due to severe epistaxis as well as an anemia requiring transfusions. In 1933 she had a linear, incomplete fracture of the left radius and ulna. Over this period, she received liver extract parenterally.

Her past history revealed that she had measles at the age of two years and that she recovered from an attack of pneumonia subsequent to influenza when she was 4 years of age.

Family History.—The mother, aged 35 years, born in Philadelphia, of Sicilian parentage, was well. The father, aged 43 years, born in the southern part of Italy, was well. Two brothers, aged 17 and 8 years, were well. There was no tuberculosis, syphilis, cancer, or diabetes in the family history. Smears of blood from the immediate family showed no nucleated red blood cells. The x-ray pictures of her 8-year-old brother revealed no bone changes. No cousins in her family were known to have the disease.

Physical Examination.—The child was a white female 14 years old. She appeared well and active; her general reaction was one of cheerfulness and cooperation. Her appearance was striking in many respects. She was thin, undernourished, and underdeveloped. Her facial appearance was mongoloid; the eyes were wide apart, the malar bones were prominent, and her skin had a bronzed color. Her height was 57 inches, weight 73 pounds (15 pounds under normal), temperature 99.3° F., blood pressure 115/75, respiration 32, pulse 112. *Head:* Her hair was black and thick. It was of the usual texture. The forehead was unusually prominent because of the frontal bosses. The head was characterized by two grooves that ran in the course of the sagittal and coronal sutures. On both sides were prominent parietal eminences. There were no areas of tenderness over the skull. *Eyes:* The eyes were not unduly prominent. There was a distinctly icteric tinge to the sclerae. The pupils reacted to light and accommodation. They were equal. *Nose:* The nose was not obstructed; there was no deviation of the septum from the midline. *Mouth and Throat:* The teeth were in a good state of repair. There were few fillings. The gums over the anterior teeth were spongy and pale. The tongue was normal in appearance. The tonsils were very large and cryptic and extended to the midline. There was a moderate amount of adenoid tissue. *Thyroid:* There was no thyroid enlargement; there was no tremor of the outstretched hand. *Chest and Lungs:* The chest showed no abnormality other than the fact that the left side was larger than the right. The ribs were prominent. The xyphoid was depressed, causing a mild funnel-shaped deformity. The lower ribs flared somewhat. The scapulae protruded and were of the wing type. There was no breast development. The lungs were everywhere resonant. There were no râles, and there were no abnormalities of the breath or voice sounds. *Heart:* The heart was enlarged to beyond the nipple line. The apex beat was palpable beyond the nipple line in the fifth interspace. There was no enlargement of the heart to the right of the sternum. The heart rate was 112 per minute at the apex. There was no thrill, and there were no murmurs. The heart sounds were regular, of good quality and volume. *Abdomen:* In the standing position, there was undue abdominal prominence which disappeared in the supine position. On the left side of the abdomen there was a linear scar 4½ inches long—the site of a previous operation. The abdomen was soft throughout. There

*Dr. Harry Lowenberg has been very kind and cooperative in consenting to have this case presented.

LABORATORY TESTS

Blood

	1933	1937	1938
Hemoglobin	52%	60%	55%
Red blood cells	2,600,000	3,500,000	3,415,000
White blood cells	*22,800	*16,600	*23,250
Nucleated reds	300/100 W.B.C.	195/100 W.B.C.	164/100 W.B.C.
Neutrophiles	51	44	34
Lymphocytes	39	54	44
Prolymphocytes			2
Eosinophiles		2	4
Basophiles			3
Monocytes			9
Promyelocytes			3
Rod nuclear			1

Mean corpuscular volume	88.2 cubic micrograms
Mean corpuscular hemoglobin	27.3 micro micrograms
Mean corpuscular hemoglobin concentration	31.0%
Volume index	0.95

Atypical leucocytes	Atypical erythrocytes
Lymphoblasts	Pronormoblasts
Promyelocytes	Normoblasts
Tuerck cells	Microcytes
	Macrocytes
	Poikilocytes

Achromia	2
Polychromasia	1
Bleeding time	7 minutes
Coagulation time	5 minutes

Blood Studies 2/19/38

Cholesterol	142	Phosphorus	5.03 mgm.
Cholesterol ratio	58	Phosphatase	21.42 units
Cholesterol ester	83	Van den Bergh	4.06 units
		Bilirubin direct delayed	

*Corrected for nucleated reds.

were no palpable masses other than the liver. There were no areas of tenderness. When the child stood, the liver reached to above the umbilicus. It was 5 inches below the costal margin in the nipple line. It was not tender. Its edge was definitely made out in the standing position. *Genitals:* There were no secondary sex changes. *Glands:* There were a few small palpable nodes in the anterior cervical groups. No other glands were palpable.

Fragility of red blood cells: Begins at 0.4 per cent NaCl and ends at 0.04 per cent NaCl. Kahn and Wassermann reactions were negative.

Urinalysis

Color was dark amber, clear, and the reaction was acid. Specific gravity was 1.009.

Other tests showed albumen, very faint trace; glucose, negative; bile, negative; and urobilin, positive in 1:10 dilution.

Microscopic examination showed occasional white blood cells; no red blood cells, and few large cuboidal epithelial cells.

X-Ray Findings.—The classical changes of this disease are present in all the bones. In the flat bones of the skull, the radiation hyperplasia is visible. The inner table is thickened and the outer table is missing. In the mandible and segments of the spine, a lacelike reticulation so characteristic in this disease is visible. In the long bones, the thin cortex, widened medulla, and irregular transverse striations near the ends are visible. There is a clublike widening of the ribs near their spinal articulations and the lower ends of the femurs have the so-called "Erlenmeyer flask" deformities. The grooved indentures along the sutures of the skull in this case have resulted from development of the bone hyperplasia after partial or complete closure of the sutures.

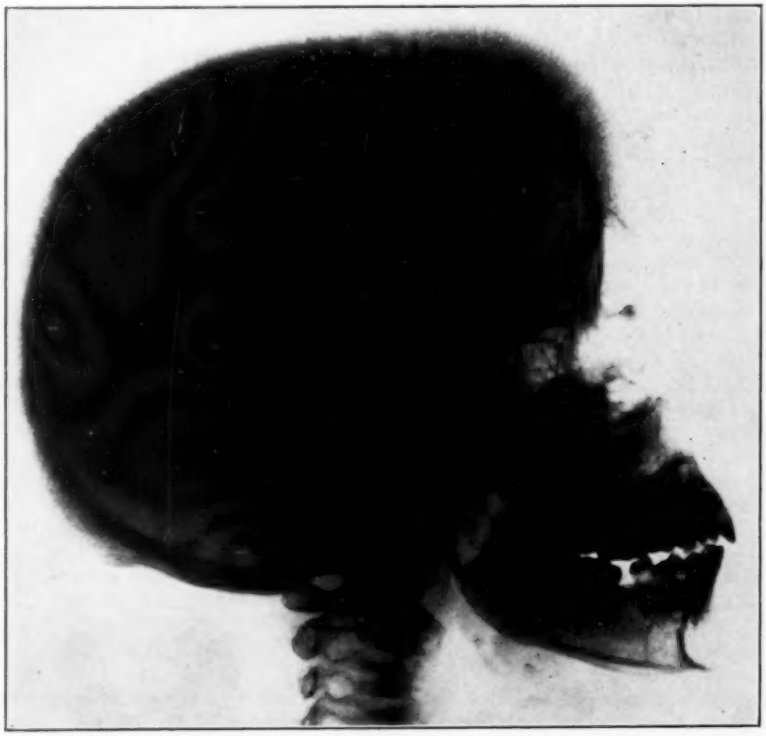

Fig. 1.—The "hair-on-end" hyperplasia of bones of the vault is marked. While the inner table appears intact, the outer table is gone and seems replaced by perpendicular strial bone overgrowth. In the mandible, the hyperplastic medulla, the thin lacy striations, and compressed cortex are all easily visible.

COMMENT

Erythroblastic anemia is a disease that occurs in early childhood, reaching a fatal issue in later childhood. We present a patient who has survived to early adolescence with relatively good health. It is our feeling that, as time goes on and as recognition of this entity becomes more prevalent, there will be more cases of adolescent or adult Cooley's anemia reported. The adult with Cooley's anemia does not present the

disease in its severest form. We are not alone in this opinion as Caffey, in presenting a series of cases, showed a few with moderate or mild bone changes. He remarked, "After following these mild cases over several years, it seems certain that such patients reach adult life and probably old age, and that mild erythroblastic anemia is not limited to infancy and childhood." We would differ with Caffey only in that the case reported here, Mandeville's case, and the case reported by Allen and Childs all presented quite well advanced changes in both the blood and the bones.

Fig. 2.—The normal compact architecture of the Haversian system of bone striations has been "washed out" by the hyperplastic overgrowth of the medulla through which there seems to course thin lacelike striations best seen in the wing of ilium and the rami of the pubis.

The child, whose case is presented here, is of Italian parentage. Her illness dates from the first year of life and has progessed with weakness and pallor from an apparently healthy infancy to a childhood with chronic illness. Her history, therefore, is typical of most children with Cooley's anemia in this respect. It differs from the usual in that she is alive at 14 years of age.

Her physical examination presents the typical findings of Cooley's anemia; a mongoloid facies caused by her yellow skin and thickened orbital bones and skull; an enlarged heart (in her case unusual in that there is no murmur); and a large protruding abdomen with a large liver (spleen removed at operation).

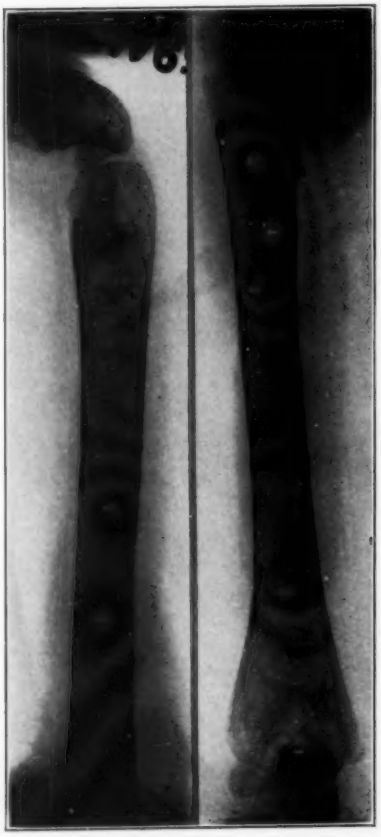

Fig. 3.

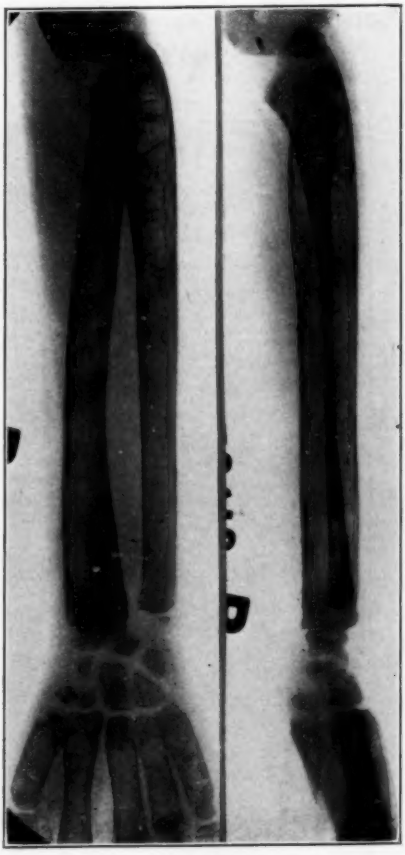

Fig. 4.

Fig. 3.—In the long bones, one sees the wide medulla, thin cortex and delicate transverse striations, more numerous near the ends.

Fig. 4.—The bones of the wrist and hand are involved like the longer bones.

The laboratory findings in this case are of interest in that they present a moderately severe anemia of 52 per cent to 60 per cent hemoglobin with as high as 300 nucleated red blood cells per 100 white blood cells. The red blood cells have numbered from 2,600,000 to 3,500,000 at various times. They are resistant to hypotonic salt solution in that fragility begins at 0.40 per cent and is completed at 0.04 per cent normal saline

solution. The stained smear of red blood cells contains all the unusual morphologic features seen in blood smears taken from children with this disease. There is anisocytosis, poikilocytosis, polychromatophilia, and reticulocytosis. One finds Cabot's rings and coarse basophilic stippling. Characteristic of the disease is the white blood cell count of 23,500 in the absence of an infection. Her serum gave a delayed direct van den Bergh reaction in common with sera from patients with anemias caused by blood destruction.

The case presented has the x-ray changes diagnostic of this disease. Attention is called to the skull with its normal inner table, thickened diploe, and missing outer table. The trabeculae radiating from the inner table do not give as typical a "hair on end" appearance as usually seen in cases with less thickened skulls. The distal ends of the femurs with their wide medullae, thin cortices, and decalcified appearance suggest the "Erlenmeyer flask" appearance described in the literature of this disease. Throughout the ends of all the long bones and the entirety of the flat bones appear the lacelike trabeculations looked for in this condition.

SUMMARY

The literature of erythroblastic anemia has been reviewed. A case in a girl of 14 years of age is presented along with x-ray studies of her bones. This is added to a series of the five previously reported cases reviewed here and one case reported to us by personal communication.

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TULAREMIA IN SIBLINGS

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IN AN early issue of The Journal of Pediatrics[1] one of us reported three cases of tularemia occurring in siblings, called attention to the extremely infectious nature of the disease and suggested that children might be particularly susceptible to tularemia. Within the past year we have observed this disease in two additional series of siblings.

Twelve cases of tularemia in patients under 12 years of age have been studied at the University of Virginia Hospital. Of these twelve cases nine occurred in siblings. This fact strongly suggests that children may be peculiarly susceptible and warrants the reporting of the following series of cases. More than one adult case in a family has been the exception in the fifty-six adult cases observed in this hospital. In one instance a husband and wife were found to be infected. While tularemia can no longer be considered a rare disease, few references to this infection will be found in pediatric literature.

Tularemia is an acute infectious disease found primarily in rodents, especially rabbits. The list of animals known to harbor *Bacterium tularense* is quite a long one and will not be discussed in this report. In 1912 McCoy and Chapin discovered the causative agent and suggested the name *Bacterium tularense*. In 1912 Francis isolated the organism from seven human cases and seventeen rabbits and gave to this infection the name tularemia. The majority of cases result from the handling of infected animals or the bite of a tick. The eating of rare meat of infected animals is a proved source of infection.

A discussion of the various clinical types of tularemia will not be included in this report. Four clinical types are recognized: the ulceroglandular, the oculoglandular, glandular, and typhoid.

SERIES I

Case 1.—W. I. J. (No. B35,830), colored female aged 8 years, was first seen in the out-patient department of the University of Virginia Hospital on May 29, 1937, complaining of a "lump" in the right and left axillary and left epitrochlear regions. Two months before admission she became acutely ill with headache, chills, fever, nausea, and vomiting. Soon after the onset of illness a mass, red and tender, was noticed in the right axilla, this mass gradually becoming less tender but fluctuant. This mass ruptured two days before admission to the hospital. One week after the onset of the illness a tender mass was also noted in the left epitrochlear region, followed in one week by swelling in the left axilla, which in time became soft and fluctuant.

There was no history of any local lesion on either hand, tick bite, or contact with any animal. There was no known exposure to tuberculosis.

From the Department of Pediatrics, University of Virginia.

Physical examination revealed a well-developed but moderately malnourished colored female, who was not acutely ill. Physical examination was essentially negative except for a walnut-sized, fluctuant mass in the left epitrochlear region. This mass was slightly inflamed and not tender. There was a similar mass in the left anterior axilla. A small indurated swelling was present in the right axilla with a small sinus from which drained purulent material. The indurated area was moderately tender, but no localized redness was noted. No other glandular enlargement was apparent, and there was no evidence of any local lesion on either hand except some old scars. Temperature was 99.8° F. rectally.

Laboratory findings were as follows: An intradermal tuberculin test with 0.1 c.c. of 1:1000 O.T. was negative in forty-eight hours. The Wassermann and Kahn tests were both negative. The urine was negative for albumin, sugar, blood, pus, and casts.

Blood studies showed hemoglobin 70 per cent (Dare); white blood cells, 11,600. Schilling differential count revealed 60 per cent segmented polymorphonuclears, 34 per cent small lymphocytes, 2 per cent large mononuclears, and 4 per cent transitional cells.

Agglutinations for tularemia gave a two-plus reaction in dilution 1:1280 in our laboratories and a positive reaction in dilution 1:2560 in a specimen sent to Dr. Edward Francis at the National Institute of Health.

X-ray film of the chest revealed a marked increase in the density of the lung markings in the mesial halves of both lungs, the changes being thought consistent with tularemia.

The patient was referred to the surgical service, where the fluctuant glands were incised and drained.

CASE 2.—G. L. J. (No. B35,827), colored female aged 5 years, was a sister of patient in Case 1. She was first seen in the out-patient department May 29, 1937, complaining of a "lump" in the left axillary region. About two months before admission, just three days after the onset of the illness of W. I. J., her sister, she became acutely ill with nausea and vomiting, high fever, but no chills. Her illness was not as acute as that of her older sister and lasted only a short time. Two weeks after the onset of the acute illness, a glandular enlargement was noted in the left axilla, which was inflamed but only moderately tender, later becoming soft and fluctuant.

There was no history of any local lesion on either hand, tick bite or contact with any animal. There was no known exposure to tuberculosis.

Physical examination revealed a well-developed but fairly malnourished colored female, not acutely ill, with essentially negative findings except for a walnut-sized, fluctuant mass in the left anterior axilla. There was no redness of the skin or tenderness. There was no other glandular enlargement or any evidence of local lesions on either hand. Temperature was 99.4° F. rectally.

Laboratory findings were as follows: An intradermal tuberculin test with 0.1 c.c. of 1:1000 O.T. was negative in forty-eight hours. The Wassermann and Kahn tests were both negative. The urine was negative for albumin, sugar, blood, pus, and casts.

Blood studies showed hemoglobin 65 per cent (Dare); white blood cells, 4,600. Schilling differential revealed 30 per cent segmented polymorphonuclears, 45 per cent small lymphocytes, 1 per cent large mononuclears, 10 per cent transitional cells, 11 per cent eosinophiles, and 3 per cent basophiles.

Agglutinations for tularemia gave a one-plus reaction in dilution 1:1280 in our laboratories and a positive reaction in dilution 1:2560 in a specimen sent to Dr. Edward Francis at the National Institute of Health.

X-ray film of the chest revealed a slight increase in the lung markings in the mesial halves of both lungs, but these changes were thought to be too slight to have any clinical significance.

The patient was referred to the surgical service, where the fluctuant gland was incised and drained, and the patient discharged after twenty days of observation and treatment.

CASE 3.—B. J. (No. B34,828), colored female, aged 18 months, a sister to the patients in Cases 1 and 2. She was first seen in the out-patient department May 29, 1937, complaining of a "lump" in the left side of the neck. About six weeks before admission, two weeks after the onset of illness in her sisters, the patient became acutely ill with a high fever, extreme irritability, and vomiting. Three days after the onset a swelling, which was neither inflamed nor tender, was noticed in the left anterior cervical region. The local physician examined the child's throat at this time and made a diagnosis of acute tonsillitis. The child continued to be quite ill with a high fever for three weeks and was fretful up to three or four days before admission.

There was no history of any lesion on the body, contact with an animal, or tick bite.

Physical examination revealed a well-nourished colored female infant, not acutely ill. Physical examination was essentially negative, except for a slight redness of the throat, and moderately enlarged tonsils. There was a mass the size of a lemon in the left anterior cervical region. This mass was fluctuant in the center, moderately inflamed, and slightly tender. The other cervical glands were palpable, but not markedly enlarged or tender. Temperature was 100.8° F. rectally.

Laboratory findings were as follows: An intradermal tuberculin test with 0.1 c.c. of 1:1000 O. T. was negative in forty-eight hours. The Wassermann and Kahn tests were both negative. The urine was negative for albumin, sugar, blood, pus, and casts. Blood studies showed hemoglobin, 60 per cent (Dare); white blood cells, 8,000; Schilling differential revealed 61 per cent segmented polymorphonuclears, 7 per cent transitional cells, and 1 per cent basophiles.

Agglutinations for tularemia gave a two-plus reaction in dilution 1:1280 in our laboratories and a positive reaction in dilution 1:2560 in a specimen sent to Dr. Edward Francis of the National Institute of Health.

X-ray films of the chest were thought to be within the limits of normal.

The patient was referred to the surgical service where the cervical gland was incised and drained.

SERIES II

CASE 4.—W. C. (No. 132729), colored male, aged 9 years, was admitted to the hospital July 1, 1937, because of a severe headache, pain in the shoulders and ankles, some stiffness of the neck, severe abdominal pain, and a general semicomatose condition of four days' duration. Three days before admission the patient complained of soreness of the neck, and a swelling was noticed in the right anterior cervical region. Since the onset of the illness there had been high fever and frequent chills, accompanied by mental confusion which gradually increased through a state of delirium to semicoma. It was difficult to arouse the child from this condition. The general picture strongly suggested typhoid fever.

No history was given of local lesions on extremities or elsewhere. There was a definite history of killing, skinning, cooking, and eating a rabbit about two weeks before admission.

Physical examination revealed a poorly nourished but well-developed colored male, appearing comatose, and lying quietly in bed. Abnormal physical findings were as follows: The skin was dry and hot; lips dry and cracked; mucous membranes pale; teeth carious, dirty, and irregular with some pyorrhea; slight tremor of the

tongue; moderate injection of the throat; right anterior cervical glands enlarged to walnut size without redness of the skin or fluctuation; some slight spasm over entire abdomen; moderate stiffness of the neck and suggestive Babinski on the right side; decreased breath sounds in right base posteriorly. Temperature was 104.2° F. rectally.

On the day of admission a diagnostic lumbar puncture was done because of suggestive signs of meningeal irritation. The fluid was found to be clear, colorless, under no pressure—showing no abnormalities after chemical and bacteriologic examination. No abnormal cytology was found. The temperature fluctuated between 102 and 105.4° F. during the patient's stay in the hospital. He never roused from his comatose condition, death occurring nine days after admission to the hospital.

Laboratory findings showed white blood cells, 10,200; red blood cells, 3,750,000; hemoglobin, 78 per cent (Haden). Schilling differential showed 22 per cent bands, 45 per cent segmented polymorphonuclears, and 29 per cent small lymphocytes. Blood Wassermann was negative. The urine was negative for albumin, sugar, pus, and casts. Blood culture was negative after seventy-six hours. On July 1 agglutinations for tularemia were negative; on July 9 they were positive in dilution 1:80.

X-ray of the chest two days after admission revealed a moderate increase in the density of the lung markings in the mesial halves of both lungs. This was interpreted as representing a bronchitis of unknown origin, but consistent with tularemia.

CASE 5.—B. C. (No. 132731), colored female, aged 5 years, was sister of boy in Case 4. She was admitted to the hospital July 1, 1937, complaining of severe headache, abdominal pain, and tender cervical glands of four days' duration. Since that time these complaints continued and grew gradually worse. There was a history of high fever, chills, and some mental confusion from the onset of the illness.

No history was given of any local lesion on the extremities, but a definite history of assisting in killing, skinning, cooking, and eating a rabbit about two weeks before admission was obtained.

Physical examination revealed a well-developed and fairly well-nourished 5-year-old colored female appearing acutely ill and quite listless. The abnormal findings were dry and hot skin, pale mucous membranes; pupils reacted sluggishly to light; slight injection of the throat; slight bilateral, tender enlargement of the anterior cervical glands, but no redness or fluctuation. The temperature was 102° F. rectally.

During her stay in the hospital, her temperature fluctuated between 101° and 104° F. for thirteen days, then began to decline gradually, reaching normal limits on the nineteenth day. Mental confusion was apparent during the first ten days of illness. She was discharged after twenty-five days of hospitalization.

During the patient's stay in the hospital there was marked increase in the size of the cervical glands, particularly on the left side, until the swelling in this area reached the size of a walnut. The glandular swelling was markedly less at the time of discharge from the hospital, with no apparent softening or fluctuation.

Laboratory findings were as follows: white blood cells, 15,900; hemoglobin, 71 per cent (Haden); red blood count, 5,040,000; Schilling differential showed 25 per cent bands and 60 per cent segmented polymorphonuclears, 15 per cent small lymphocytes. Blood Wassermann test was negative. The urine was negative for abumin, sugar, blood, pus, and casts. The blood culture was negative after seventy-six hours. Agglutinations for tularemia were as follows: On July 6, three-plus in dilution 1:10; on July 9, three-plus in dilution 1:20; on July 14, two-plus in dilution 1:40; on July 19, one-plus in dilution 1:60; later positive in dilution 1:5160 at the laboratories of the National Institute of Health.

An x-ray picture made two days after admission revealed a moderate increase in the density of the lung markings in the mesial halves of both lungs. This was interpreted as being bronchitis of unknown etiology but consistent with tularemia.

The patient was discharged after twenty-six days of hospitalization, with cervical glands still enlarged but otherwise apparently recovered from the acute infection. Although advised to return to the out-patient department, the patient has not been brought back since her discharge.

CASE 6.—E. C., (No. 132730), colored female, aged two years, sister of patients in Cases 4 and 5. She was admitted to the University of Virginia Hospital on July 1, 1937, complaining of headache, abdominal pain, nausea and vomiting of four days' duration. Fever had been high, with increasing mental confusion.

There was no history of local lesions on extremities or trunk, but a definite history was given of assisting in killing, skinning, cooking and eating a rabbit about two weeks before admission.

Physical examination revealed a well-developed colored female, obviously acutely ill, lying quietly in bed. The abnormal findings were as follows: dry and hot skin; pale mucous membranes; moderate injection of the throat, marble-sized bilateral enlargement of the anterior cervical glands. The temperature was 103° F. rectally.

During hospitalization the patient's temperature was septic in character, fluctuating between 101 and 105° F. for thirteen days, entirely subsiding by the eighteenth day of hospitalization and remaining so until discharge on the twenty-sixth day. During her stay in the hospital the cervical glands became tender and walnut-sized though never fluctuant. No periods of mental confusion were noted.

Laboratory findings were as follows: white blood cells, 15,400; hemoglobin, 60 per cent (Haden); red blood cells, 4,600,000. Schilling differential count showed 19 per cent bands, 40 per cent segmented polymorphonuclears, 36 per cent small lymphocytes, and 5 per cent large mononuclear cells. Blood Wassermann test was negative. The urine was negative for albumin, sugar, pus, and casts. Blood culture was negative at forty-eight hours. During hospitalization the following agglutinations for tularemia were obtained: On July 6 a two-plus in dilution 1:20; on July 9 a two-plus in dilution 1:20; on July 15 a one-plus in dilution 1:80; on July 19 a one-plus in dilution 1:160; and on the same date in the National Institute of Health laboratory a positive agglutination in dilution 1:1280 was obtained.

Two days after admission x-ray pictures of the chest revealed a moderate increase in the density of the lung markings in the mesial halves of both lungs. This was interpreted as bronchitis of unknown etiology, but consistent with tularemia.

After being in the hospital for twenty-six days, the patient was discharged with cervical glands still enlarged, but apparently she had recovered from the acute infection. Although advised to return to the out-patient department, the patient has not returned since her discharge from the hospital.

SUMMARY

Six cases of tularemia in siblings are reported.

Attention is called to the highly infectious nature of tularemia and the suggestion is made that children may be particularly susceptible.

Two of the reported cases are of particular interest because of age alone, the disease occurring at the ages of eighteen months and two years.

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ACUTE POLYNEURITIS OF UNCERTAIN ORIGIN (GUILLAIN-BARRÉ SYNDROME)

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IN 1916 Guillain, Barré and Strohl[1] first described a neurologic syndrome which they differentiated from the previously recognized polyradicular neuritides. They called attention to certain findings characteristic of this symptom complex in the two patients they reported. These cardinal findings were (1) motor disturbances, (2) loss of tendon jerks, (3) preservation of cutaneous reflexes, (4) paresthesia with slight disturbance of objective sensibility, (5) tenderness on pressure of the muscles, (6) little change in the electrical reactions of the nerves and muscles, and (7) hyperalbuminosis of the cerebrospinal fluid in the absence of cytologic reaction. Hyperalbuminosis was regarded as the most significant of the observations in this polyneuritic syndrome. Succeeding reports of observations of this condition appeared entirely in the European medical literature, and in 1936 Guillain[2] presented a résumé of ten previously unreported cases (all in adults) and an excellent bibliography of cases of the same condition reported by others up to that time. The disease was considered essentially one of adult life, usually in individuals between the ages of 20 and 50; in children and old persons it was thought quite rare. Batten,[3] Harris,[4] and later Ford[5] reported single cases of chronic polyneuritis of unknown origin in children; the children reported by the two latter recovered. Hecht[6] in 1937 presented seven cases which he designated as "acute infective polyneuritis." The seven cases had widespread and symmetrical paralysis or paresis of lower motor neuron type. The spinal fluid of each, with one exception, showed hyperalbuminosis in the absence of cytological reaction. All of the patients but one made complete recovery in periods varying from a few weeks to many months.

We are reporting in this paper a case of acute polyneuritis occurring in a child in whom the findings fulfilled the requirements cited by Guillain. Judging from reports in the literature, this type of polyneuritis is rarely seen in childhood. This case is of special interest in that improvement and recovery followed complete removal of numerous abscessed teeth.

CASE REPORT

D. J., a boy, aged 6 years, was first seen at the clinic Feb. 10, 1938, at which time he complained of "paralysis" since Jan. 20, 1938. The father and mother were alive and well. There had been no other pregnancies, and the family history

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was essentially negative. He had been delivered at term and the birth history was negative. His developmental history was normal. He had always lived in Indiana. He had had mumps and measles in a mild form when he was four years old. Since July, 1937, he had been troubled with frequent gumboils and toothaches. He had not been immunized. In December, 1937, he complained of his stomach. The pains were not severe but became very frequent. There was constipation but no nausea or vomiting. At the same time he had some discomfort in the calves of his legs and a little headache, but he was not ill enough to be in bed. About the first week in January it was noted that he was weak and unable to walk well. He had had little or no fever. A doctor who saw him advised that two carious teeth be extracted, and this was done. In the three weeks prior to his admittance to the clinic, he became completely helpless, being unable to sit, stand or walk. There had been no loss of bowel or bladder control. No history of ingestion of arsenic or lead in any form could be elicited in the history.

Physical examination showed a slender, malnourished, apathetic, irritable boy. His height was 47¾ inches (191 cm.), and weight, 44 pounds (17.6 kg.). The average weight for his height and age was 52 pounds (23.6 kg.). The pulse was 104, and the rectal temperature, 99.5°. He had many carious teeth, and his tonsils were of moderate size, fibrotic, and infected. No lead line was noted on the gums. There was moderate generalized lymphadenopathy. Examination of the heart, lungs, and abdomen was negative. He could not stand alone and was completely helpless, being unable to sit up, turn over, or hold up his head without support. He could not move the upper or lower extremities except for the fingers. Flexion of the back was painful. Deep reflexes were all lost; abdominal and cremasteric reflexes were elicited. The Babinski sign and ankle clonus were absent. No definite sensory changes could be elicited. Moderate atrophy of all muscles was present, and there was mild muscle tenderness, particularly in the calves of the legs. Examination of the fundi by the ophthalmologist showed narrowed retinal arteries and essentially normal disks. The pupils were unequal, the right being larger than the left. Reaction to both light and convergence was poor. It was not possible to test accommodation. Examination of the teeth and dental x-ray studies by the dentist showed that almost all his teeth were carious. The upper deciduous incisors and lower molars had been removed. A small fragment of the lower right deciduous first molar was present in the mouth of the socket. Fig. 1 is a photograph of the boy at the time we first observed him.

Urinalysis on several occasions was negative. The blood count showed a hemoglobin of 82 per cent, erythrocytes 4,020,000, and leucocytes 5,950 of which 50 per cent were lymphocytes, 2 per cent monocytes, 43 per cent neutrophiles, 3 per cent eosinophiles, and 2 per cent basophiles. There was no stippling of the red cells. Coagulation and bleeding time were within normal limits. The blood Kahn and Rytz tests were negative as was the Mantoux test with 0.1 mg. of old tuberculin. The phenolsulphonphthalein test showed 88 per cent dye excretion in one hour. Tests for arsenic and lead in the urine, feces, and hair were negative. Roentgenographic studies of the skull and chest were negative; the long bones showed no evidence of a lead line. Spinal puncture was done Feb. 15, 1938. The fluid was clear and under normal pressure. Queckenstedt was negative. Wassermann of the spinal fluid was negative. There were no cells, colloidal gold showed 0000122200, and the Pandy test was strongly positive.

The patient was given large amounts of vitamins A, B, C, and D without change in his general condition over a period of several weeks. On Feb. 29, 1938, tonsillectomy and adenoidectomy were done. The small fragment of the right deciduous first molar was lifted out at the same time. Unfortunately no cultures were made of the tonsils or tooth. Following this, there was a slight improvement in the use of

his hands and feet. He had a toothache several times in the succeeding three weeks, and on March 19 all deciduous teeth except those showing little or no caries were removed; this included all the upper molars except the right second molar. A month later, when the boy was seen at the clinic, he had made striking progress, and the parents said he had improved "40 per cent." He was crawling on the floor, had gained weight, and was eating better. On Aug. 7, 1938, he began to take steps alone and by Sept. 1, 1938 was walking without support. There was at that time 90 per cent return of all muscle function, but the deep reflexes were still absent. Wrist drop had disappeared, but there was no improvement in ankle drop.

Fig. 1.—Note the inability to hold the head up or sit erect. Ankle drop is evident.

DISCUSSION

The acute polyneuritides of unknown origin are generally regarded as infectious, probably due to a neurotropic virus, although there is little substantiating evidence. Some investigators believe the damage is done by a toxin without direct invasion of the nervous system by an organism. In some cases there has been a sore throat, a gastro-intestinal upset or mild malaise preceding onset of symptoms. At other times occurrence of paralytic symptoms is abrupt. Barker[7] reported a case in a child following an abscessed tooth. The disease has been generally regarded as one of adult life. When onset is acute,

there is a striking resemblance to Landry's paralysis, but the distribution is peculiar in that the paresis frequently involves proximal groups of muscles more than distal groups and is strikingly symmetrical. The paralysis is flaccid and is usually associated with hypotonia. Muscular atrophy is less marked than in the other recognized forms of infectious and toxic polyneuritides. The deep reflexes are abolished while in contrast the cutaneous reflexes are maintained. The sensory changes are varied; at times there is spontaneous pain, cramping, and occasionally paresthesia and numbness. In certain instances paralysis of a cranial nerve occurs, but the mental condition is quite normal and as a rule consciousness is not altered. Attention has been called to the frequent association of facial diplegia with this form of polyneuritis; involvement of other cranial nerves is rare. In the true symptom complex described by Guillain, the prognosis is generally good. The course is variable and the degree of paralysis may fluctuate from time to time. The paralysis may be rapidly progressive for two to five days followed by complete recovery within a few weeks. The usual type runs a more chronic course with gradual return to complete or partial activity over a period of months or even years. Recovery has usually been complete in the experience of most observers. In certain other forms of infective polyneuritis not uncommonly the patient may die within a few days from paralysis of respiratory centers or sudden collapse probably due to cardiac failure.

There are little data on post-mortem studies inasmuch as patients generally recover. Hyland and Russell[8] found the anterior horn cells in the spinal cord rounded and shrunken. The Nissl granules were pyknomorphic and had a tendency to clump in the center of the cells. Anterior nerve roots, peripheral nerves, and intramuscular nerves showed severe demyelination. Posterior nerve roots and sensory nerves in muscle spindles showed little change. All peripheral nerves showed proliferation of the interstitial tissue and were infiltrated by mononuclear cells. Their case fulfilled the requirements of Guillain except for the spinal fluid. Since spinal puncture was never done the case cannot be rightly designated as the Guillain-Barré syndrome. Likewise in the post-mortem studies by Bradford, Bashford, and Wilson,[9] few spinal punctures had been done, making the findings as regards this particular syndrome less informative.

Polyneuritis must be differentiated from poliomyelitis. The case reported herein occurred at a time when there was no known poliomyelitis in the vicinity. The absent or minimal fever and the marked symmetry of the lesions pointed away from the diagnosis; also the positive Pandy test of the spinal fluid in the absence of any cytologic reaction was against poliomyelitis. He was likewise thoroughly examined for lead and arsenic poisoning. There was no suggestion of vita-

min B deficiency, and the sweating, photophobia, and skin changes of acrodynia were absent. Recovery is the rule in this particular type of polyneuritis, and consequently the relation to removal of teeth may be coincidental. Nevertheless, little or no improvement was noted following removal of two teeth on one occasion and tonsillectomy and adenoidectomy at another time. It was after the complete removal of all the remaining decayed teeth that improvement began almost immediately.

CONCLUSION

A case of extensive flaccid paralysis occurring in a child has been described. It is thought to belong to a group of cases described in the literature variously as "acute infective polyneuritis" or "radiculoneuritis." It is a typical example of an uncommon but more clearly defined syndrome described originally in the French literature as a type of infective polyneuritis. The apparent rapid improvement and eventual recovery following the extraction of numerous, carious, deciduous teeth is most unusual.

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TUBERCULOUS ATELECTATIC BRONCHIECTASIS

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THAT pulmonary tuberculosis in childhood may contribute to the etiology of certain cases of bronchiectasis was previously suggested by Lightwood and Wilson.[1] In the present report the clinical and pathologic data concerning a case in which tuberculosis was a proved etiological factor are presented.

S. K., a boy aged 6 years, was well until 4 years of age, when he began to have recurrent attacks of bronchitis with severe cough. At five years of age he had measles and bronchopneumonia. For one month prior to admission he had a persistent cough with loss of appetite and weight. Recently there had been a small amount of frothy sputum and occasional night sweats were noticed. The father, who had an active case of pulmonary tuberculosis, was in contact with the child until one month before the child's admission.

On clinical examination it was noted that the boy was poorly nourished. He had a persistent cough, occasionally productive of sputum. The fingers were not clubbed. The temperature was irregularly raised to 99° F. Inspection of the chest showed equal movement on the two sides. The percussion note, however, was impaired at the right base, and the breath sounds over this area were distant and accompanied by a few moist râles.

X-ray examination (Fig. 1) revealed a triangular opacity at the right base which suggested collapse. The lipiodol injection (Fig. 2) showed a collapsed and mildly bronchiectatic right lower lobe. As it was considered from these findings that this was probably a case of mechanical bronchiectasis secondary to a bronchial stenosis, a bronchoscopist was consulted. This examination was undertaken by Mr. James Crooks, who reported narrowing of the right lower bronchus due to the presence of a thick grayish membrane. A specimen of this was taken for biopsy.

Pathologic Report.—Histologic sections taken from the specimen showed granulation tissue and large areas of necrosis with some calcium-containing tissue. The Ziehl-Neelsen stains revealed definite acid-fast organisms, having the morphology of *Bacillus tuberculosis.*

Laboratory Examination.—The intradermal tuberculin test (Mantoux) was positive in dilution of 1:1,000. The sedimentation rate was 12 mm. (normal 2 to 10). Red blood cells numbered 4,100,000, the white blood cells 10,900. The hemoglobin was 75 per cent; color index, 0.9. There were 72 per cent polymorphonuclear leucocytes; 24 per cent lymphocytes; and 4 per cent eosinophiles. Sputum examination failed to reveal any acid-fast organisms.

Treatment and Progress.—Carbon dioxide inhalations failed to re-expand the lobe. Tipping did not produce any appreciable increase in the amount of the sputum. The temperature and cough gradually subsided with rest in bed, and the child was sent away for continuation treatment at a convalescent home. Six months later a lipiodol x-ray investigation showed that the lobe had entirely re-expanded and the dilated bronchi had resumed their normal shape (Figs. 3 and 4).

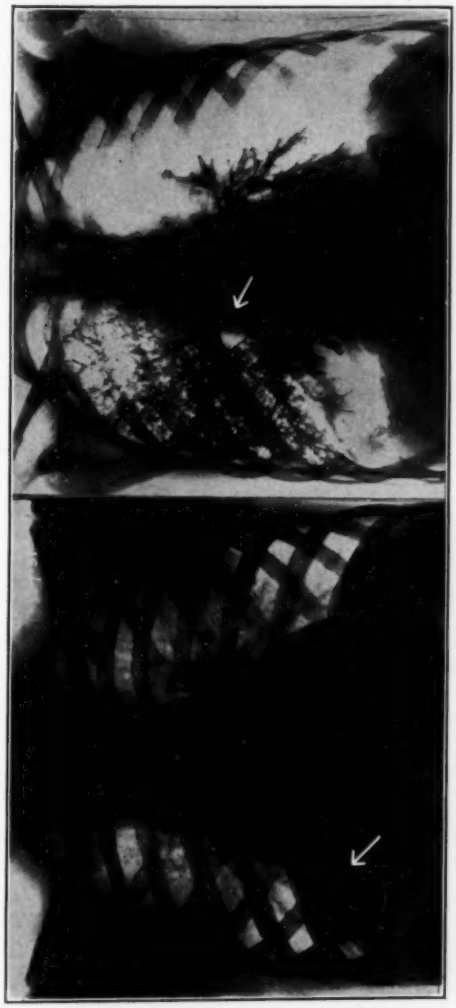

Fig. 1.

Fig. 2.

Fig. 1.—Flat plate of the chest showing the triangular opacity at the right base due to the collapsed right lower lobe.

Fig. 2.—Lipiodol injection which shows obstruction of the right lower main bronchus with bronchiectatic dilatation of the air passages distal to this.

DISCUSSION

Etiologically the interpretation of this case is similar to the one previously reported by the author[1] and also to cases reported and discussed by others.[2] Prosoroff[3] and Morlock and Pinchin[4] have recorded cases of so-called epituberculosis, in which they demonstrated a similar pathology. They did not demonstrate the accompanying bronchial dilatation or suggest the possibility of termination in bronchiectasis. The finding of x-ray evidence of bronchiectasis in this case suggests that tuberculous stenosis of the bronchus caused the

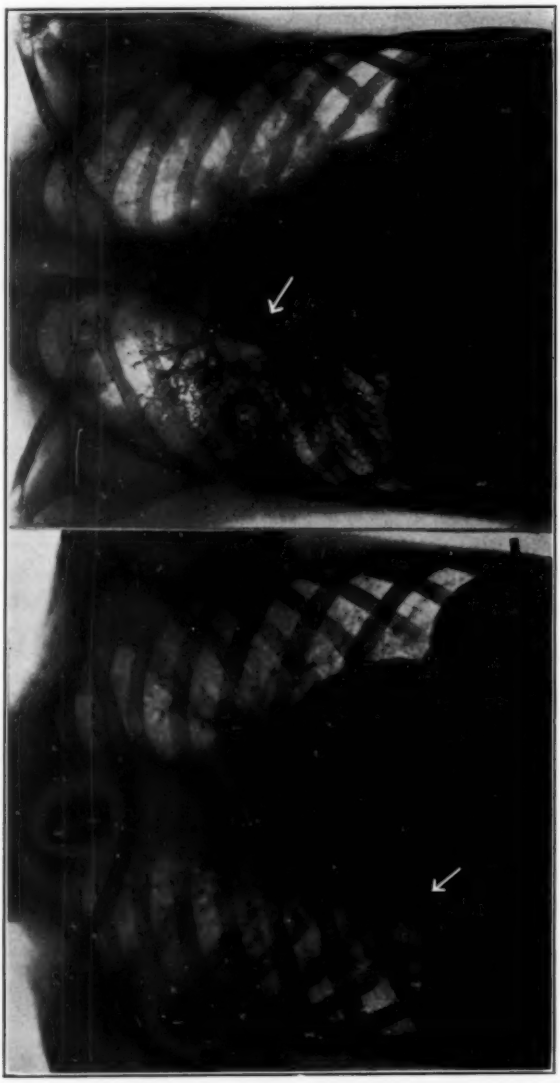

Fig. 3.

Fig. 4.

Fig. 3.—Flat plate of the chest after constitutional treatment, showing re-expansion of the right lower lobe.
Fig. 4.—Lipiodol examination which shows the right lower lobe re-expanded and the bronchial obstruction relieved.

collapse and that the bronchi underwent secondary dilatation. The family history, positive skin reaction, and demonstration of the organisms in the granulation tissue make tuberculosis a certain causative agent. From the author's previous experience[1] such lobes may undergo extensive fibrosis, and it was thought that re-expansion of the lobe was unlikely. However, in the present case, under general constitutional treatment, the tuberculous process in the bronchus ap-

parently healed and allowed the lobe to re-expand and function. Secondary infection of such a lobe may give rise to a genuine purulent bronchiectasis with later involvement of other lobes. If the lobe does not re-expand with adequate constitutional treatment as it did in this case, some of these early cases may be suitable for lobectomy. That children withstand this operation very well has previously been demonstrated.[5] Some authors have noted that aspiration of the caseous material which causes the stenosis may allow a more recently collapsed lung to re-expand and function.

The author wishes to thank Dr. Donald Paterson of the Hospital for Sick Children (London) for permission to publish this case and for his helpful advice.

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TRYPTOPHAN BODIES IN TUBERCULOUS MENINGITIS

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TRYPTOPHAN bodies are said to be increased in tuberculous meningitis. Based on this, a test has been devised to differentiate this from other forms of meningeal irritation. Baxter[1] found that the spinal fluid of every one of his 41 cases of meningeal tuberculosis gave positive tryptophan reactions; the fluid from all of his 32 control cases gave negative reactions. The spinal fluid in 30 of the 32 cases of tuberculous meningitis seen by Spilane[2] gave positive reactions; his 25 cases of tuberculous joints without involvement of the meninges gave negative tests; and 86 cases, normal or with neurological involvements other than tuberculous, gave negative reactions. He stated that the tryptophan test was useless if the spinal fluid was purulent, hemorrhagic, or xanthochromic. Only 3 spinal fluids from Giustra's 10 cases of tuberculous meningitis were positive;[3] 2 spinal fluids from 25 cases of nontuberculous involvement of the central nervous system were also positive. Guglielmin[4] tested 29 specimens of cerebrospinal fluid. Eight which were obtained from cases of tuberculous meningitis gave positive reactions. The remaining 21 specimens gave negative reactions although there were pseudopositive reactions in one case of suppurative meningitis and in 2 cases of xanthochromia.

Since 1932 we have performed tryptophan tests on the spinal fluids obtained from many cases with various forms of meningeal irritation. This is a report of our results.

The diagnosis of tuberculous meningitis in 55 cases was proved in each instance. In 25 cases (45.6 per cent) the diagnosis was confirmed at autopsy. In the remaining 30 cases, the organisms were actually found in the spinal fluids, or their presence was demonstrated at autopsy examination of guinea pigs which had been inoculated with the spinal fluids. When guinea pigs were injected, at least 2 were used for each spinal fluid, and tuberculosis had to be found in both animals.

There were 147 control cases, 74 of which were diagnosed as cases of bacterial meningitis. Seventy-three cases showed other meningeal conditions. The diagnosis in cases caused by bacteria was proved by demonstrating the organisms in all but one instance. Cases of noninfectious meningeal irritations such as poliomyelitis, aseptic meningitis, disseminated myelitis, encephalitis, brain tumor, encephalomyelopathy, subdural hematoma, cerebral arteriosclerosis, and Simmond's cachexia were diag-

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nosed by typical clinical signs, laboratory findings, or post-mortem. Thirty-four of these cases were autopsied.

RESULTS

The spinal fluids of 202 cases were studied. Twenty-one, or 38.1 per cent, of the spinal fluids from the 55 cases of tuberculous meningitis gave positive tryptophan tests while 34, or 61.8 per cent, gave negative tests. Thirty-five, or 23.8 per cent, of the spinal fluids obtained from 147 nontuberculous cases gave positive tryptophan tests, while 112, or 76.2 per cent, gave negative tests (Table I).

TABLE I

Cases of tuberculous meningitis in which tryptophan test was positive (3 negative in course of disease)		21
Cases of tuberculous meningitis in which tryptophan test was negative		34
Cases other than tuberculous meningitis in which tryptophan test was positive		35
Epidemic meningitis	15	
Pneumococcus meningitis	5	
Streptococcus meningitis	5	
Influenzal meningitis	3	
Brain tumor	2	
Cerebral accident	2	
Disseminated myelitis	1	
Miliary tuberculosis	1	
(?) Septic embolism	1	
	35	
Cases other than tuberculous meningitis in which tryptophan test was negative		112
Epidemic meningitis	25	
Streptococcus meningitis	9	
Pneumococcus meningitis	5	
Influenzal meningitis	6	
Aseptic meningitis	4	
Unqualified meningitis	1	
Staphylococcus meningitis	1	
Poliomyelitis	12	
Encephalitis	16	
Disseminated myeloencephalitis	2	
Encephalomalacia	1	
Pachymeningitis, subdural hematoma	1	
Cerebral arteriosclerosis	1	
Hemorrhage into caudate nuclei	1	
Subarachnoid hemorrhage, cause ?	1	
Simmond's cachexia	1	
Cerebral arteriosclerosis and atrophy of brain	1	
Negative lumbar punctures	24	
	112	
Total		202

COMMENT

The tryptophan test was negative when theoretically it should have been positive in over 60 per cent of the cases of tuberculous meningitis and was positive when it should have been negative in over 23 per cent of the cases of nontuberculous meningeal irritations. The test was found to be negative in 76.2 per cent of the cases of nontuberculous meningeal irritations when it should have been negative. This seemed suggestive

until we noted the fact that it was positive in only 38.1 per cent of the cases of tuberculous meningitis.

CONCLUSION

We have used the tryptophan test on 202 spinal fluids to try to differentiate tuberculous meningitis from other forms of meningeal irritation. We agree with Giustra[3] that the test is valueless as an aid to differentiate tuberculous from other forms of nontuberculous meningeal irritation.

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RENAL CALCIFICATION IN INFANCY AND CHILDHOOD

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DURING the course of a study of calcium deposits in the kidney in a large series of autopsies, calcification was found to occur with surprising frequency in infants and children. A study of thirty-one such cases is presented to clarify the etiological factors and the significance of such calcification.

Reported cases of renal calcium deposition appear to fall into three groups: (1) those apparently dependent upon hypercalcemia and excessive calcium excretion by the kidneys; (2) cases of dystrophic calcification, where localization of the mineral deposit is in degenerating or necrotic tissue, without the aid of hypercalcemia or excessive calcium salt excretion; and (3) cases in which there is a hypercalcemia or excessive calcium excretion and, in addition, some injury or degenerative change in certain cells of the kidney which determines the localization of the deposit.

Examples of Group 1, true metastatic calcification, are exceedingly rare. It may be that some cases of acute hyperparathyroidism should be grouped here. Some doubt may be felt that even in such cases there is lack of toxic renal injury. The difficulty of producing hypercalcemia and renal calcium deposits by simple excess ingestion or injection of calcium salts is well known.

In Group 2 are classed those cases of calcification following chemical injury to tubular epithelial cells, as in bichloride of mercury poisoning. Here also should be considered the important cases associated with disturbances in the acid-base balance of the blood and nephrotic changes, usually as the result of high intestinal obstruction. Nazzari[1] in 1904 drew attention to renal calcification associated with pyloric stenosis. The publication of Brown, Eusterman, Hartman, and Rowntree[2] in 1923 pointed out the definite injury to tubular epithelium of the kidney which occurs in cases of high intestinal obstruction. These degenerative changes and the accompanying calcification were further emphasized by Cooke.[3] Severe toxemias or infections may also cause degenerative changes in kidney tissue leading to calcification, though some other factor seems necessary, and most of such cases properly belong in the third group. Marked calcium deposits associated with local infections of the kidney have been noted by Crabtree[4] with colon organisms, and by Albright, Dienes, and Sulkowitch[5] with *Hemophilus influenzae*.

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Group 3 includes the cases of chronic hyperparathyroidism, whether due to a primary adenoma of the parathyroid glands or secondary to a chronic renal insufficiency or pituitary disturbance. It would appear that the renal calcification resulting from hypervitaminosis D must also be included in this group.

Renal calcification as it occurs in infancy and childhood has been infrequently reported. Mitchell,[6] in his review of renal dwarfism, noted frequent interstitial calcium deposits, many of which were of the type which has been pointed out to be characteristic of chronic hyperparathyroidism. Thatcher[7] described the calcium deposits in a fatal case of hypervitaminosis in a child. Marsden[8] pointed out renal calcification in an infant in association with a severe infection. In the cases reported by Butler, Wilson, and Farber,[9] there was persistent dehydration, acidosis, terminal pneumonia, and renal calcium deposits.

In the thirty-one cases composing the present report age varied from 7 days to 11 years. In eleven cases there were only very slight amounts of calcium, either as a single deposit, or two or three small calcified masses. These masses were mainly intratubular, either in the cortex or the medulla, but occasionally were interstitial. Careful study of the clinical history and autopsy findings in these minimal cases indicated no cause or relationship of any of the clinical or anatomical abnormalities to the renal calcium deposits. In the remaining twenty cases where the calcification was more massive, the clinical and autopsy findings appear to be of some significance. A short outline of these twenty cases is presented.

REPORT OF CASES

CASE 1.—A white female infant, aged 3 months, was premature and presented a feeding problem. During the last month she had a mild continuous fever, and some pus was noted in the urine. Autopsy study showed little, other than mild inflammatory and degenerative changes in the urinary tract. The microscopic appearance of the kidney tissue was distinctive. There was a mild granular degeneration of cortical tubular epithelial cells. Massive deposits of calcium were present in the pyramids, mostly within tubules, but in many instances being outside tubular epithelium. This peritubular calcium frequently distorted the tubular lumen and occasionally broke through to form tiny calculi in the tissue of the medulla.

CASE 2.—A colored girl, aged 9 years, received many extensive burns sixteen days before death. This was followed by the development of extreme toxicity, dehydration, vomiting, and evidence of renal damage, with oliguria, albuminuria, casts, and a few red cells. At autopsy the kidneys were found very pale and acutely swollen. Microscopic study showed marked degenerative changes in renal tubules, particularly of the cortex, with some interstitial lymphocytic cell infiltration. The calcification was limited to the cortex and was mainly intratubular with involvement of degenerated epithelial cells and also the formation of calcium casts.

CASE 3.—A colored male, aged 8 months, died six days after the onset of acute bronchopneumonia. The urine showed fine granular casts. The kidneys showed degenerative changes in the tubules and moderate numbers of intratubular calcified casts limited to the cortex.

CASE 4.—A negro boy, aged 3 years, who was weak, had failed to gain weight properly and was subject to frequent vomiting attacks. During the month before death he vomited daily, sometimes many times daily. There was clinical evidence of renal involvement, with albumin, granular and hyaline casts in the urine on repeated examinations. The nonprotein nitrogen of the blood rose as high as 92.3 mg. per 100 c.c. The child was emaciated and dehydrated. Autopsy showed a nonrotation of the colon with a congenital abnormality of the mesenteric attachment of the small intestine and proximal one-third of the colon. The actual point of obstruction was at the duodenojejunal junction. The duodenum and stomach were greatly dilated. The kidneys showed massive calcification, almost limited to the cortical region. The calcium was mainly intratubular, with involvement of epithelial cells. A moderate degree of nephrosis was present.

CASE 5.—A white female, aged 4½ years, was ill for eight weeks, during which time she showed signs of infection and involvement of the central nervous system. The urine reaction was acid. She was given 15 gr. of calcium lactate daily for the ten days preceding death. The autopsy diagnosis was epidemic encephalitis. The cortex of the kidney contained a moderate number of intratubular granular cast-like calcium masses. Some of the tubules showed mild degenerative changes.

CASE 6.—A colored female, aged 6 months, died of miliary tuberculosis. She vomited frequently during the 3 weeks preceding death and was markedly dehydrated. The urine was acid and showed some albumin and granular casts. The kidneys showed a moderate number of intratubular calcium masses with mild nephrotic changes. The calcium deposits did not appear to bear any relation to miliary tubercles in the renal tissue.

CASE 7.—A negro boy, aged 4 years, died of miliary tuberculosis with tuberculous meningitis. The urine was acid. The kidneys showed moderate calcium deposition in cortical tubules, with associated mild nephrotic changes, but bearing no relation to miliary tubercles.

CASE 8.—A white female, aged 4 months, suffered from dehydration, with diarrhea, respiratory infection, and some vomiting. Autopsy showed bronchopneumonia and a diphtheritic and ulcerative colitis. The kidney tubules show degenerative changes and a small number of intratubular calcium deposits.

CASE 9.—A white female, aged 7 months, died following a severe three-week illness, with otitis media and pneumonia with abscess formation. She vomited frequently during the illness. The urine was acid and contained albumin and pus cells. The kidneys showed marked degenerative changes in tubular epithelium, and a moderate intratubular calcium deposition in the cortex.

CASE 10.—A white boy, aged 4 years, was admitted to the hospital two months after an attack of scarlet fever with signs and symptoms of nephritis. The blood pressure was elevated. Nonprotein nitrogen of blood was 159 mg. per 100 c.c. Autopsy showed the kidneys to be involved by a subacute nephritis, with an occasional intratubular calcium deposit in the cortex. There were also vascular and interstitial changes in the kidneys.

CASE 11.—A white female, aged 14 days, died of otitis media and bronchopneumonia. Microscopic study of the kidneys showed marked degenerative changes in the tubules of the medulla with calcification of desquamated epithelial masses. The cortex was free from calcium deposits.

CASE 12.—A white male, aged 7 days, died of meningitis and bronchopneumonia following repair for spina bifida. On the day preceding death he was given 9 minims of parathyroid extract and 30 c.c. of a 10 per cent solution of calcium gluconate. The kidneys showed very numerous cortical deposits of calcium in tubules, in the

lumina and walls of small blood vessels, and in interstitial tissue. Moderate nephrosis was present but did not appear to be important in determining the localization of the calcium deposits.

CASE 13.—A white male, aged 6 months, was admitted to hospital with vomiting, diarrhea, and mastoiditis. The urine was acid and contained albumin and fine granular casts. The kidneys showed mild nephrotic changes and a few small intratubular masses of calcium in the cortical region.

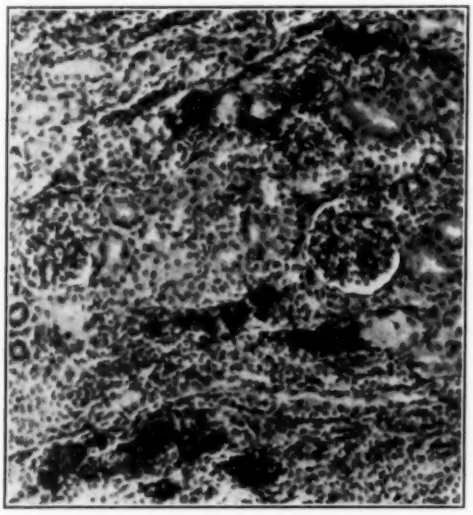

Fig. 1.—Photomicrograph of renal cortex, Case 16, showing the intratubular calcium masses.

Fig. 2.—Photomicrograph of renal cortex, Case 20, showing masses of calcium within tubules and small blood vessels.

CASE 14.—A negro girl, aged 1 year, suffered from epileptiform attacks for seven months before death. The urine was acid and contained some pus cells. She was given daily ultraviolet radiation, and received a total of 2 c.c. of parathyroid extract and 135 c.c. of 10 per cent calcium gluconate. Renal calcification was marked, and practically confined to the cortex. The calcium deposits were mainly intratubular, but many were intravascular and interstitial. Some nephrotic changes were present, but not clearly associated with the calcium deposits.

CASE 15.—A white male, aged 40 days, developed convulsive seizures at three weeks of age. During the course of treatment he was given 1.5 c.c. of parathyroid extract and 10 c.c. of 10 per cent calcium gluconate. Autopsy showed intracerebral hemorrhage and terminal pneumonia. The kidneys showed a moderate interstitial and intratubular calcification involving the cortex.

CASE 16.—A negro girl, aged 1 year, suffered from dehydration, acidosis, and an acute upper respiratory infection. At autopsy the kidneys were found to be swollen and pale. Microscopically tubular degenerative changes were seen. An area of massive calcification was present in the cortex, involving mainly convoluted tubules.

CASE 17.—A white male, aged 7 months, a mongolian idiot, suffered from otitis media, parenteral diarrhea, acidosis, and dehydration. Autopsy showed terminal pneumonia. The kidney showed moderate nephrotic changes with a moderate intratubular calcium deposition, involving the lining epithelial cells and limited to the cortex.

CASE 18.—A negro boy, aged 7 years, was admitted to hospital with abdominal pain and vomiting, associated with a ruptured appendix and paralytic intestinal obstruction. Operative drainage was performed, but obstruction and vomiting continued. Autopsy showed a moderate nephrosis and some intratubular calcium deposition limited to the kidney cortex.

CASE 19.—A negro female, aged 7 months, a congenital syphilitic, suffered from upper respiratory infection, diarrhea, acidosis, and dehydration. Autopsy showed bronchopneumonia and a fairly massive cortical intratubular calcium deposition.

CASE 20.—A negro male, aged 8 days, showed muscle twitchings and numerous widespread hemorrhages. During the course of treatment he received 1 c.c. of parathyroid extract, 5 c.c. of 10 per cent calcium gluconate parenterally, and 18 gr. of calcium lactate. Autopsy showed moderate degenerative changes in renal tubular epithelium and massive intratubular and intravascular calcium deposits in the kidney cortex.

DISCUSSION

In practically every case the main calcium deposition was within the tubules. There were calcified masses in the tubular lumen, but invariably involvement to some extent of the lining epithelial cells. The deposits were found mainly in the convoluted tubules of the cortex but not invariably so, as occasionally the collecting tubules at the base or even at the apex of a pyramid were involved. In four cases there were in addition calcium thrombi in cortical arterioles and capillaries. It would appear significant that each of these four patients having peritubular intravascular calcification had received repeated administration of parathyroid extract and calcium salts a short time before death. The occurrence of peritubular calcification in hyperparathy-

roidism has already been pointed out. In one case calcium salts alone were administered, and here the renal calcium was entirely intratubular.

Two patients had intestinal obstruction accompanied by excessive vomiting and urinary findings indicating renal damage. In one of these cases, in which the obstruction was at the distal end of the duodenum, the clinical and autopsy picture was comparable to that of the cases reported by Brown, Eusterman, Hartman and Rowntree[2] and by Cooke.[3] Here there was particularly severe renal calcification.

Seven patients had histories of moderate repeated vomiting, associated, except in one case in which there was extreme toxemia due to extensive burns, with an acute infection. In the cases in which the urine was examined a short time before death, abnormalities were usually noted, with variable amounts of albumin, casts, and cells.

In most of the cases the reaction of the urine was found to be acid. It is well known that tissues having an acid secretion, such as stomach, lung, and kidney, are particularly prone to calcium deposition. With acid secretion the tissue cells are left in a relatively alkaline state, under which circumstances calcium compounds are less soluble and may precipitate. The work of Kleinmann[10] has indicated that acid diets may cause great changes in the renal excretion of calcium and phosphate, and he was able to induce renal calcification by the addition of acid to a high calcium diet. Kleinmann[11] has also demonstrated alkalinity in degenerating and necrotic tissues. Mild to severe degenerative changes are seen in tubular epithelial cells in the majority of the cases reported here.

In five cases there were dehydration, acidosis, and acute pneumonia, resembling in many respects the cases described by Butler, Wilson, and Farber,[9] though differing in that there was always some vomiting or diarrhea, and the renal calcium deposit always involved tubules. In Butler, Wilson and Farber's cases of persistent dehydration, acidosis, terminal pneumonia and renal calcium deposits, some of the calcium masses were adjacent to tubules, resembling in this respect the deposits in hyperparathyroidism. There is some indirect evidence that acidosis may possibly act as a stimulus to parathyroid hyperplasia and hyperfunction.

CONCLUSIONS AND SUMMARY

Deposition of calcium in the kidney occurs frequently in infancy and childhood in association with a variety of conditions. Occasional small deposits appear to be of no significance.

Twenty cases of marked renal calcification in infants and children are briefly reported. The calcium was most frequently limited to the cortical region and involved tubules. In four patients who had re-

ceived parathyroid extract and calcium salts, the calcium was also found in small blood vessels.

Evidence of renal damage, both clinically and at autopsy, was almost invariably found.

Acute infection, intestinal obstruction, dehydration, and acidosis were each present in a number of cases. Each seemed to be a factor of importance in certain cases. Vitamin D administration was not an important factor in the renal calcification in any of the cases reported here.

The author wishes to acknowledge the kindness of Dr. E. C. Mitchell, Professor of Pediatrics at the University of Tennessee, College of Medicine, in giving permission to use the clinical records of the Pediatric Service of the John Gaston Hospital in the preparation of this paper.

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A DEVICE TO AID IN THE FLUOROSCOPY OF INFANTS

JOSEPH HARMAN FRIES, M.D.
BROOKLYN, N. Y.

THIS portable stand has been found useful in the fluoroscopic examination of infants in the upright position.

It consists of a wooden platform erected on a simple upright metal stand, about three feet tall. The wooden platform holds two metal uprights, each consisting of a pair of hollow brass cylinders, one sliding within the other. A screw device at the base of the tubes permits adjustment to any desired height. The *U*-shaped metal prongs fixed to the upper ends are covered with rubber tubing. The upright bars are set into the platform by means of a screw and bolt arrangement. The bolts pass through perforations in the wooden platform and are secured by screws to the undersurface of the board.

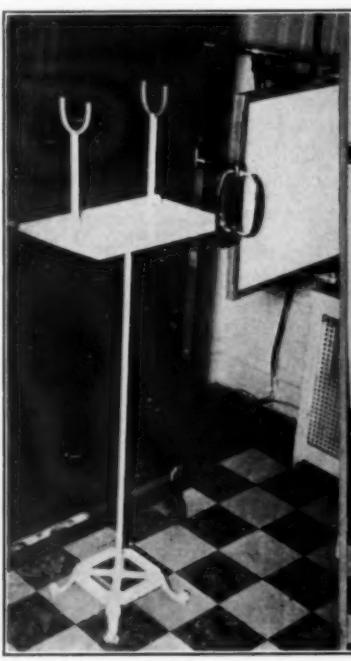

Fig. 1.

Fig. 2.

The child is maintained in an upright position, between the roentgen tube and the screen, by supporting his arms over the arm rests. The panel of the fluoroscope serves as a posterior rest for the patient.

A NEEDLE GUIDE AND BLOOD COLLECTION APPARATUS

ROBERT COHEN, M.D.
LOUISVILLE, KY.

COLLECTING blood intravenously for serologic, biochemical or bacteriologic purposes by the syringe-needle combination has met with, and still is in, favor today both among the doctors and technicians.

These two devices are not introduced to replace the syringes but to serve as an addition to the armamentarium in hospitals and physicians' offices.

This apparatus is both a needle guide and blood collector, depending on the use to which one puts it. For collecting blood, the test tube is inserted into the cap, or the semicircular cuff; the needle is put on the metallic adapter. With the thumb rest held for firmness, the device is ready for intravenous insertion.

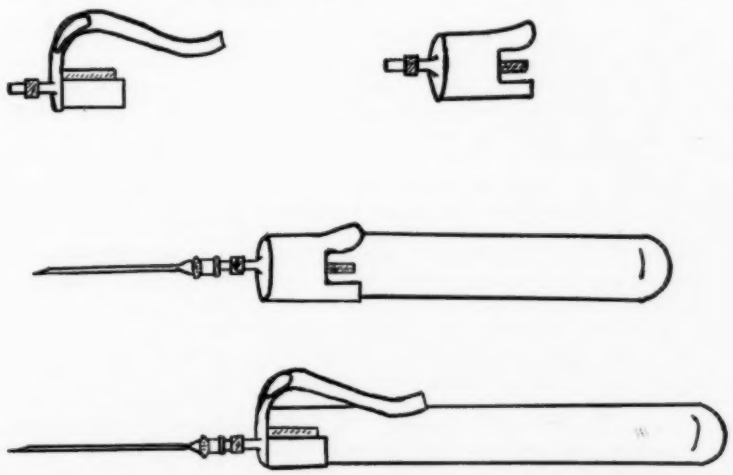

Fig. 1.—Top, models before attachment. Bottom, models after attachment to test tubes.

For use as a needle guide, the needle is put on the adapter with the thumb on the wider portion as a rest and the index finger below it. It is now ready to perforate the vein. It is easily removed from the needle when blood returns through the adapter. Then a cannula attachment for intravenous infusions replaces the guide, or a large syringe with hypertonic solution can be inserted in its stead.

The advantages of these instruments are economy and convenience in that they are not breakable and are easily sterilized; their use eliminates

an added step of pouring the blood from the syringe into the test tube, thus avoiding early clotting and the possibility of contamination.

The principle of both is about the same. Galvanized tin is made into a cap to snugly cover the mouth of a test tube. It is ½ inch deep with four springy phalanges as ¼ inch extensions to hold the test tube firm. One phalanx is a little broader than the others for a thumb rest. The second device has a right angle bend (appears streamlined). The horizontal wing or thumb portion is 1½ inches long by ¾ inch wide. The vertical portion is ¾ by ¾ inch. At the bend a hole is punched out in order that visibility may be obtained. A semicircular cuff ½ inch long to hold the test tube is soldered at the inner lower surface of the vertical portion. To both apparatus metallic adapters are soldered in the center and through the vertical caps.

Figs. 1 and 2 show the simplicity of the needle guide and blood collecting device.

4207 West Market Street

American Academy of Pediatrics

Proceedings

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 9, 1938

Round Table Discussion on School Health Problems and Relation to Pediatrics

Chairman: Dr. Harold H. Mitchell, Long Island City, N. Y.
Assistants: Dr. Herbert R. Stolz, Oakland, Calif.
Dr. Arthur E. Wade, Seattle, Wash.
Dr. Estella Ford Warner, Albuquerque, N. M.

CHAIRMAN MITCHELL.—On my way to this meeting I picked up a popular magazine and read, "It is becoming increasingly apparent to the public at large that there is something radically wrong with the medical set-up in this country." Whether we like it or not, it is obvious that the spread of such an idea and the proposals accompanying it will soon result in political agitation. Certainly few physicians believe any good will come either to the public or medical service from the politicians' interest. Above all things the medical profession fears political interference and bureaucratic domination and the loss of freedom to determine medical policies.

I do not believe medical leaders are lacking. Such leadership is found in the field of medical education, scientific research, hospital organization, and in a host of other fields. It is possible that physicians have given too little attention to the education of the public in the proper use of the medical resources of the community and to developing newer ways for the distribution of medical care. Although we are faced with confusion and ferment, I believe medical leadership can maintain its right to determine its own policies.

The health services in the schools are undoubtedly going to expand in one form or another. It is a field that the pediatrician can and should do something about. In theory at least it has been regarded as fundamentally educational in character. But lay domination and the neglect of medical leadership have led to a blurring of the educational objective, low medical standards, and trends towards actual competition with the other medical facilities of the community.

The comments from the members of the Academy which came from the questionnaire of last year showed bitter disapproval of a policy of employing obstetricians, gynecologists, pathologists, nose and throat specialists and even politicians as school physicians. Pediatricians objected to the false sense of security that parents get from the school service. They criticized the authority assumed by those nurses who work without medical guidance, as well as diagnosis and actual treatment by the school nurse. They objected to the tendency to train parents and children to rely on free service when they could afford private care. They objected to the lack of investigation of cases referred for free care and the competition of

free toxoid and vaccination promoted through the schools. Again and again there were vague references to competition and the encouragement of socialization and state medicine through the schools.

There were also indications of appreciation of the contribution of this service to the education of the public and to the avoidance of medical neglect. It seemed apparent from a review of all the comments that the complaints were generally directed toward a growth of activity which had very little or no medical guidance. A large proportion criticized the quality of medical service as superficial, lacking in medical histories, and poor in medical judgment. With neglect of the quality of service, lay domination, and so little real medical leadership, the school health service is peculiarly exposed to the development of policies that will conflict with medical principles and with the education of the public for sound medical care. So it seems clear that this round table group should consider what might be done about it.

One of the members of the committee here went into the position of director of the Seattle School Health Service as a full-time physician through the efforts of the local pediatric society. The activity of the Seattle pediatricians had been concerned with the improvement of the service. This interest of the pediatricians had won the confidence of the school authorities and the public. The pediatricians were aggressive in the interest of the public and of the school health program so that their support had great influence in assisting Dr. Wade in developing sound policies. Dr. Wade, won't you tell us more about the Seattle situation?

DR. A. E. WADE.—There is a philosophy in school medicine which distinguishes it from private practice. It involves making the schools safe places for children, seeing that no part of the school's program injures any child, educating the children in healthful living and health knowledge, counseling with those in charge of child guidance and maintaining a liaison between the parents of the children and the medical and dental professions.

School medicine should not practice the art of healing. It should perform a service of conservation of health. It is bounded by the triumvirate, state health laws, public health, and the medical profession and carries their messages and directions to the schools. Executed properly, it must be manned by a highly trained personnel. School medicine is rapidly becoming a medical specialty. Already, postgraduate courses are being offered by a few of our medical colleges.

Educators and physicians are becoming cognizant of the need of a mutual understanding. A working relationship is being developed. Perhaps the dual relationship of the private physician's physical examination and the school physician's physical examination has been the most provocative of misunderstandings. Some schools have analyzed this question and offer solution by a statement of purpose in these examinations. It is best that the school physical examination be made with the purpose of securing for the school information regarding physical and mental endurance and capacity. This information is usable in determining the need for individual modification of the school program. The private physician's physical examination, by its nature, should be made with the purpose of securing for the child or his parents information regarding physical and mental departures from the normal. This information is usable in diagnosis and treatment. Thus, the school physician and the private physician would find themselves performing entirely different types of examinations. These two distinct types do not conflict in any way but aid each other. A well-arranged method of communication between the school physician and the private physician could make these dual examinations profitable to both. Schools where this statement of purpose has been announced report an unprecedented interest on the part of physicians in the community and a higher standard of health among the pupils.

Realizing the importance of developing school medicine in accordance with this philosophy, the Pediatric Society of Seattle took steps, three years ago, to secure the appointment of one of their members to the office of director of health in the schools. This was accomplished by the pediatrists enlisting the influence of the county medical society and recommending such appointment to the board of education. The appointment was made. Through conferences between the county society and the school health personnel, a classification was made regarding what medical services should be administered by the schools and what should be administered by organized medicine. A wholesome relationship now exists. The physicians of the city are interested in their patients' welfare in school and the schools are interested in the welfare of the pupils when under the care of the physicians. The general health of the children has improved. The school physicians have more time to devote to health education. The curriculum pertaining to health matters is better supervised. Truly, the Seattle schools are profiting by this alignment with the medical men. The excellent work of Dr. Harold Mitchell and his committee has contributed much to the success of the present program.

CHAIRMAN MITCHELL.—In considering what they have done in Seattle, Detroit, and many other places where organized medicine has taken an active interest in the school health program, it has seemed to me that an aggressive but sympathetic committee of your county medical society or a group of pediatricians might guide local policy so that the work of the physician in the schools could be developed in a manner to satisfy the most aggressive advocate of the socialization of medicine and still retain the approval of the most conservative defender of private practice. With such complete coverage of all pupils in the schools we could follow up and see that no child suffered from medical neglect.

If we consider the proposals that came from our questionnaire for caring for the children able to employ a private physician, those who can afford only part cost, and the indigent, we see that medical guidance could prevent conflict and competition. Then the nurse and school doctor with the help of the school organization could guide parents in a proper use of the medical resources for children of the community better than through any other organization.

On the other hand, if organized medicine does not take any more interest in school health service in the next ten years than they have taken in the last twenty years, it is likely that the changes will be quite in conflict with medical policies and we will have lost our opportunity to develop the kind of educational program that is needed.

If I might take a few more moments at this time, I wish we might consider further the complications of improving the quality of school service. The physician who works in the public schools too often has been in bad repute because his examinations were misrepresented to the public. The school authorities and the public expect him to give a full and complete health examination and then require more examinations than he can possibly do in the limited time allotted. Parents either get a false sense of security from the school examinations, or else the service is in such bad repute that they disregard important advice regarding neglected children.

For many years the physician who works in the public schools has faced a dilemma. If he examines all the children he is asked to examine, he must cut down on the time spent on each pupil. If he spends plenty of time on each pupil, then he cannot examine all the pupils. He wants to give his best possible judgment about the child's needs in his school environment, but if he takes the time for this he cannot see every child. He would like to interpret to the teacher the amount and kind of work which the child can carry, but such interpretations require individual study that requires more time. If the child has some disability or a potential handicap, he would like to give some prognosis to the parents or indicate clearly the possibilities of med-

ical service, but too often he is under pressure and must make a snap judgment about each case in order to cover large numbers.

Physicians with high standards of medical service are interested in improving school medical service, and they are the ones who understand that it is a poor educational policy to let the public believe that the school medical service is an adequate substitute for the individual personal service which the physician can give in his office. The school service should be presented as a limited or partial service. If we as physicians are to maintain high standards of quality of medical service, we must insist that the schools clearly define the limitations of the school service. We must not allow the public to believe that a two- or three-minute examination, or even a five-minute or ten-minute examination, can take the place of the continued individualized service of the personal physician who cares for the child in sickness and in health.

Organized medicine has no desire to limit the preventive and educational service of the physician and the nurse in the schools, but the time has come when the medical profession should speak out against the sacrifice of quality to quantity. With the best of intentions the layman will demand more and more medical service regardless of deficient quality that may come from an overload upon the physician. We must recognize that neither the educator nor the parent will know when quantity has crowded out quality. When the physician in school has so many children to examine that he cannot give the individualized study necessary to give advice that meets high medical standards, then it is essential that organized medicine demand that the limitations of the school service are clearly defined.

For many years the importance of employing a physician and nurse for the schools was not appreciated. Such service was regarded as one of the frills of education. During this period while we were gaining recognition of the importance of the school medical and nursing service, we have tried to improve the service by adding more staff, but now that the school authorities and the public recognize that every school should have medical and nursing service, we do not need to emphasize the number of children served as much as we need to protect the quality of the service. It is time now also to emphasize the fact that the school physician does not attempt to take over the responsibility of the practitioner and he does not displace the practitioner in the field of health supervision and health examinations.

We should try to educate for high ideals of health service; we should recommend continued medical supervision with systematic periodic assessment of the individual healthy child and guidance in the further nurture and training of the child by the medical practitioner. But the school should not pretend that rapid inspections by the school physician meets this need. Education for healthful living should set high ideals just as we present the highest cultural and ethical training in our educational system even though all may not be able to take advantage of the best that our educational institutions afford.

In order to influence the health educational program toward high ideals of health service, to suggest opportunities for training in health attitudes, to make the medical examination educational, and to select what is important and to reject the unimportant health education subject matter, the physician must be more than a mere inspector or examiner. He must be a real advisor on all health matters in the school. To be this he must learn to talk the educators' language and have time to participate in curriculum building and to become familiar with all that is going on in the school. In fact he should come to understand educational philosophy and principles. Then he can become a real school medical advisor.

Another member of our committee has given special attention to this field of health education. Dr. Warner, I understand, has recently tried out a plan for bringing the local physician into closer touch with the school program, and, as she

has acted as medical advisor to guide the the health education of the teachers, she has also succeeded in getting the local physicians to participate.

Dr. Warner, will you tell us about this experience with the Indians?

DR. ESTELLA WARNER (ALBUQUERQUE, N. M.).—In our work we aimed at a health education program only. The physician is responsible for certain phases of the program but neither he nor the nurses do any classroom teaching. This is left entirely to the teachers. All the doctors in the communities who so desire have been invited to share in the work. Their advice is sought, and the patients are referred to them. Conferences are held every two months with the entire staff, including teachers. The program is made up jointly by this group, the physicians' main function being to advise and to teach the teachers. On the subject of tuberculosis, for instance, he instructs the teachers on the cause, mode of spread, and methods of combating. The program has been in existence only a year.

CHAIRMAN MITCHELL.—Dr. Bierman also instituted health education in a new region. May we hear from her?

DR. JESSIE M. BIERMAN (WASHINGTON, D. C.).—In Montana there were practically no school physicians in the state, and the doctors were generally opposed to having them. It was therefore suggested that in the larger county medical societies a committee of five doctors interested in school health be appointed to work with the schools and school nurses to develop an educational health program. These physicians were generally opposed to mass examinations in the school. Entering pupils were therefore all sent to physicians, or if they could not afford private care they went to the county physician and obtained a health record. There was a very good response from both physicians, schools, and parents even the first time it was tried.

CHAIRMAN MITCHELL.—May we hear about your work in Oakland, Dr. Meyers?

DR. EDITH M. MEYERS (OAKLAND, CALIF.).—In Oakland the school health service is regarded primarily as a unit in the educational system. We aim at all times to keep clear of therapeutics; and even diagnosis is not a prime object. Our school doctors are not urged to do anything more than to determine whether or not a child deviates from the normal and, if he does, to steer him into the proper channels for a correction. These points must be constantly stressed with children, with teachers, and with parents. To educate the teacher to recognize among her pupils tendencies toward deviations from normal, to educate the parent as to the need for further examination and treatment of these deviations, and to educate the child to lead a life within his handicaps are the educational functions of our Oakland School Health Service.

The machinery for carrying out this program, while it varies in some respects in each school in the city, we have found to be most successful where some such plan as this is practiced:

The classroom teacher, from her observations for unusual behavior, scholastic failure, poor attendance, poor physical appearance, or any other characteristics of this nature, refers the child to the doctor with a résumé of her observations. The doctor's examination includes as a very important feature a fairly complete history and family history (particularly in the case of behavior problems). In younger children this may have to be supplemented by the parent.

At the close of the doctor's half day at the school, a conference is held with the doctor; the nurse, if the school has a nurse; the dean; the physical education teacher; and counselors, if possible; all in attendance. All information is pooled, and a suitable adjustment is made. If there is a physical defect, a note goes home to the parents advising them of such; if there is a question of finances, the nurse

investigates and gives information regarding clinics; if a school program change is in order, the dean or the counselor arranges it; if the home program seems at fault, the parent is asked to call to confer with the doctor.

The findings and settlement of the case go back to the counselor for her use in advising the child further, and to the original classroom teacher who referred the case. If the adjustment made concerns any other teachers in their relations to the child, they too receive the information.

We have found this program entirely satisfactory, and opening as it does an entirely new field to the school health department, that is, the services of the school physician as an advisor in guidance problams, we have kept his role within the scope of an educational system.

CHAIRMAN MITCHELL.—Before proceeding, will you tell us, Dr. Stadtmuller, about the preschool round-up?

DR. ELLEN S. STADTMULLER (SAN FRANCISCO, CALIF).—The National Congress of Parents and Teachers has changed its policy in regard to the summer round-up, endeavoring to send the preschool child for physical examination to the office of the family doctor rather than encouraging the group method of physical examination in the schools.

If members of the Academy of Pediatrics wish to foster this plan of the national group, they need to enlist the help of the organization itself. By proceeding from the state president to the seventh vice-president, who is the director of health, and then to the summer round-up chairman, they will have authoritative backing within the organization. By meeting with the state chairman of summer round-up to assist her in her planning, they can help outline the program of work which is distributed by the state chairman to the individual school units. These outlines of work carry definite instructions to the unit chairman responsible for summer round-up and, if specifically worded, will tend to throw the whole plan to the offices of private physicians.

CHAIRMAN MITCHELL.—It might be of interest if I told something more about the school health study in New York City. This study is being conducted in the district where I am district health officer. This is one of the thirty health districts into which New York City is now divided for convenience in administration. The school health study is privately financed and is directed by a committee of which our Academy president, Dr. Van Ingen, is chairman. The committee is made up of representatives of both the Department of Health and the New York City Board of Education and also others eminent in medicine, public health, and education. The procedure is to try out ways of conducting the school health program in eight schools that might be practical for application to the whole city. You will appreciate that New York City is so large that any changes that are not real improvements are very costly to carry out; data are gathered and each procedure is studied and analyzed. The failures and inefficiencies are given as careful attention as success and efficiency.

This spring we have been experimenting to see if we could improve the service for undernourished children. We found the nursing staff particularly concerned about this problem because their files were overloaded with nutritional deficiency cases, many of which had been carried for a long time without improvement. The school physician had selected the cases as undernourished, but from this point the responsibility fell on the nurse. She was faced with the problem of convincing the parent that the child should have further medical care. She often must convince the mother that the child's condition could be improved, and, when the parent wanted to believe the child was all right, she might try to impress upon her that there was real risk in delay or even try to alarm the mother.

From previous studies, of course, we were aware of the fact that not all of these children selected as undernourished were equally in need of attention. In fact there is bound to be in such a group a great discrepancy of opinion as to the nutritional status of the children selected. And for those truly undernourished, there was a great variety of factors which contribute to their condition and hence a variety of ways for meeting their need. There were poor children who suffered from an inadequate diet as well as children from well-to-do homes where poor appetite and lack of parental control were the principal factors.

The complexity of the situation made it clear that it was not enough to send a notice nor to have the nurse give the parent a talk that generalizes on the subject of poor nutrition. A great deal more must be known about each case. The parent must be given reasons for believing the child is undernourished. Physical signs and symptoms must be noted in order to back up what is told the parent about the seriousness of the condition. A medical history and study are necessary to learn something about the etiology. With such more thorough knowledge of the case we might follow it through to obtain proper care.

We started on the experiment by asking the regular school physicians to work up their nutrition cases as they would work them up in private practice. Medical histories were obtained, repeated observations were made; the etiological factors were studied; and the opinion of the physician was recorded for recommendations as if he were going to prescribe the treatment. We recognized that so thorough a study of each case was probably beyond the scope of the school service, but it seemed necessary to depart from the limited knowledge of the cases that had been so inadequate in obtaining results. A well-trained pediatrician was assigned to review the cases and to guide the procedure.

This experience was of such interest to the physicians and revealed so many cases of long-continued medical neglect that the thoroughness of the procedures was justified. Then other children were selected on the basis of whether it was likely that they could be benefited. Observations were made, and histories were obtained which were sufficient to make the parents understand that there was real evidence of nutritional deficiency. Cases in which there was inadequate food because of poverty were referred to social agencies with definite recommendations. Bad health habits which were likely to interfere with good nutrition were discussed with the mother, and definite advice was given whenever the case could not be turned over to the private physician for supervision. To work up these cases the parents were invited to the school or to the health center for interviews. When the parent could not be seen at school, the physician visited the parent in the home. Conflict with private physicians or clinics was avoided by prescribing no treatment and referring all cases for any continued medical attention, except cases referred to social agencies when there was inadequate food because of poverty, and except for the simplest advice about the more obvious health habits and about the improvement of the diet in cases where medical care was an economic strain.

Where a private or clinic physician had already seen the child, but was not giving care, the case was referred again for further attention, and in many such cases the practicing physician was contacted to supplement the history or to explain the findings of the school physician and the reasons for referral. Such contacts often brought to light medical conditions not understood by the parent and recommendations of the private physician which could be adjusted through the school or other resources of the community. The resourcefulness of the school physicians in guiding parents to make a proper use of the school and medical facilities was thus a revelation of the scope of the service that might be carried out by the nurse. It gave the physicians an opportunity to see ways that they might advise and assist the nurse to do her job better. Then the physicians could point out how children might obtain the medical care needed without conflict or competition with the private or clinic facilities.

This experience was recognized as so valuable by the central office of the Department of Health that arrangements have been made for all the school physicians who are available during the summer to work up more of the more serious cases in the files in which the children had not responded to the previous efforts of the nurse.

We believe this approach to the nutrition cases will result in such a clear understanding of the whole problem by the school physicians that they can make a better selection for follow-up. They will select on a basis of whether the children are likely to benefit from follow-up. The experience has brought out the value of a medical history and a study of the case so that the physicians can advise the nurse how to meet these complex problems with more knowledge than a mere symbol or crude classification of the nutritional status. While the school physicians can hardly meet the full need for study of etiological factors and health supervision to correct the causes of undernourishment, it seems clear that further consideration of the different kinds of cases before initiating the expense of follow-up would enable the school physician to guide the nurse without the waste effort of so much undiscriminating advice to parents.

DISCUSSION

DR. WADE.—When health education is the main object, defects become by-products of the work. The doctor examines the child and his health records for information for himself in order that he may guide correctly the deaf, the spastics, the poor readers, etc. There is a line of communication between the doctor and school. Teachers and nurses are instructed how to detect signs of illness, and the family physician reports on the child to the health officer. The nurse sees that the child returns to his private physician as often as is necessary.

DR. C. G. ASHLEY (PORTLAND, ORE.).—It is hard to get away from some practice of medicine in the schools. Coaches are demanding children be certified for athletics. They do not see the educational part of the program.

CHAIRMAN MITCHELL.—Suits are brought against boards of education for accidents. School boards feel strongly about protection.

DR. WADE.—Our staff examines every boy before any equipment is issued. This is done three times a year. Every boy in athletics is insured in the County Medical Society Service Bureau. Football players pay $1 a month, others 50 cents. If a boy cannot afford this, the athletic fund provides for it. The insurance covers hospitalization, x-ray examination, drugs, etc., and the doctor's care. This method has been in operation three years, and there have been no law suits.

DR. A. U. CHRISTIE (SAN FRANCISCO, CALIF.).—Have you a legal right to refuse to issue equipment to a boy who is handicapped?

DR. WADE.—Yes.

CHAIRMAN MITCHELL.—Schools are usually willing to follow the recommendation of the physician.

DR. CHRISTIE.—I asked this question because to my knowledge a boy with rheumatic heart disease was permitted by school authorities to play football, the advice of the medical staff being disregarded.

CHAIRMAN MITCHELL.—This comes back to the relationship between physicians and educators. Usually school boards are very afraid of sudden death in a child. This brings up the question of the amount of diagnostic work and the facilities for it that we should have in the school.

DR. WADE.—In every case of a heart murmur we confer with the family doctor first, before reporting anything to the patient. We do try the functional test of hopping, taking the time it takes for the heart rate to return to 90. If any pathologic condition is present, the permission of the family doctor, as well as that of the school physician, is obtained for any extra activity.

DR. E. J. LAMB (SANTA BARBARA, CALIF.).—We have brought a cardiologist into the schools in a consulting capacity. She examines the child under question, and the note to the parents goes out with the signatures of two doctors.

DR. H. F. HELMHOLZ (ROCHESTER, MINN.).—Many parents have been frightened over insignificant murmurs. The school physician needs to be very careful.

CHAIRMAN MITCHELL.—If the family physician does not agree with the verdict, it hurts the school program. Calling the private physician in on the problem as Dr. Wade has done is good. The school then recommends sending the child back for continued supervision. It is a great field for give and take.

DR. MEYERS.—We have more difficulty with the child who has been labeled once as cardiac by a doctor and who continues thinking he is one. It becomes the school physician's function to try to cure the neuroses. The sole object of health services in the schools should be educational. The facilities in the community provide anything needed for the care of indigent patients to private patients. The doctor is the agent for disseminating this information to the parent, child, and teacher.

DR. CHRISTIE.—What method can be used for screening out children needing medical care? How much time should a doctor allot per child to do an adequate health examination? How much money should be spent per child in an ideal health service?

DR. G. D. CARLYLE THOMPSON (PORTLAND, ORE).—When making hurried examinations of large numbers of children, a doctor is very likely to overlook some pathologic condition; and this tends to put a school physician in disrepute. Many volunteer physicians refuse to give their services for this reason.

DR. CHRISTIE.—Can the height-width-weight tables be used to pick a group needing more concentrated attention?

CHAIRMAN MITCHELL.—This picks only one group, and underweight by such tables is hardly a basis for selection to refer to the family physician or for follow-up by the nurse. No doubt we need screening devices to pick the group needing more concentrated attention, but in my experience none of the weight tables are among the most useful screening procedures.

DR. THOMPSON.—In Astoria the teachers have a screening chart. It is simple, and the teacher is taught how to fill it out. On it are listed several things such as mouth breathing, poor vision, speech defects, and irritability. The doctor should have at least ten minutes per child.

CHAIRMAN MITCHELL.—How about vision and hearing?

DR. LAMB.—What use can be made of the ophthalmograph?

DR. CHRISTIE.—I think it belongs in larger centers with experts.

DR. HELEN B. PRYOR (PALO ALTO, CALIF.).—One has been used in the Menlo School for Boys.

CHAIRMAN MITCHELL.—In addition to these tests, there is the question of tuberculin testing, Schick testing, and immunization.

DR. WADE.—We use the tuberculin test only for high school entrants and require a letter of permission from the parents first. The tests are done by the Department of Health, and the family physician alone gets the report. Physicians send patients in for testing and x-ray plates.

DR. ASHLEY.—Portland is doing one school at a time, and the reports are sent directly to the physician.

DR. HELMHOLZ.—The purpose should be to discover a tuberculous environment and source of the infection should be emphasized to the parents. The onus should be taken from the child, placing it on the source of the infection.

DR. BIERMAN.—It is futile to do any work unless it can be properly followed up.

CHAIRMAN MITCHELL.—It comes back to what is worth while considering the budget allowed for it. How about immunization in the schools? Some have recommended 1 c.c. of alum-precipitated toxoid to all children entering school who have been inoculated in early infancy. What is the opinion of this group?

DR. CHRISTIE.—In Toronto 22 per cent were positive after one dose.

DR. ASHLEY.—In Portland immunization is done by the health department.

DR. THOMPSON.—This should be a part of the preschool rather than school program and the P.T.A. might be used to see that children are immunized before they start school.

DR. LAMB.—The schools might do the Schick tests to determine the percentage immune, and the immunization could be done by the department of health, clinics, or private physicians.

DR. H. E. THELANDER (San Francisco, Calif.).—Detroit has apparently succeeded in keeping a high rate of immunization without doing any in the schools.

DR. MEYERS.—I think money can be spent to greater advantage in health education than in the practice of medicine in schools. Teachers can be taught to detect evidence of poor health and to refer these children to the school physician. An hour can be set aside for discussion of these cases with teachers, counselors, and nurses. In this way the child is helped and adjusted, and the teacher becomes more alert to the possibility of a physical basis for a child's failure.

CHAIRMAN MITCHELL.—I am in sympathy with the move to have such conferences with teachers.

DR. LAMB.—I think the conferences are excellent. We do the same thing in child guidance, remedial reading, and sight-saving classes.

DR. MEYERS.—We should not limit ourselves to physical health but project our interest into mental health as well. Educators are anxious for help in this field.

DR. WADE.—I think the most important work is guidance.

DR. HELMHOLZ.—Other lay groups also welcome guidance.

CHAIRMAN MITCHELL.—In other words, the physician should be more than an inspector and examiner. He has been forced to assume this role because he has not been very effective in guiding the health program. He has accepted demands for examinations when he should have refused so that he might have time for guidance. If extension continues along the line of trends that we see in many schools, he will have to do more and more treatment and less guiding of policies. Of course, the doctor will not make the program educational by giving talks to the children nor by assuring that he can take over the teacher's function, but he can tell the teacher, the principal and the superintendent many things they should know about health.

In fact, if he ever gets started on health guidance, he must usually watch for an opportunity to offer health advice and explanations.

DR. WARNER.—We have a health institute for teachers—neither the doctor nor the nurses do classroom teaching although they may demonstrate certain phases to the students. Thus the 9-year-old group is taught infant care by demonstration. A doll is used first for bathing, dressing, and then the demonstration is made with a real baby. The teaching is progressive and is taught naturally as the subject arises. The information is more likely to be remembered if given when the question has come up.

CHAIRMAN MITCHELL.—This method gives the proper attitudes and can be used to dispel many superstitions.

DR. PRYOR.—In a recent study carried out as a thesis for the degree of Ph.D., it has been determined that interest in child care and training is keenest at the junior high school age. More attention should be given to the teaching of subjects at the age level when interests in that subject is highest.

GILBERT J. LEVY, M.D.
H. E. THELANDER, M.D.
Secretaries.

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 10, 1938

Round Table Discussion on Rheumatic Fever

Chairman: Dr. T. Duckett Jones, Boston, Mass.
Assistants: Dr. Robert L. King, Seattle, Wash.
Dr. Morse J. Shapiro, Minneapolis, Minn.

The Treatment of Rheumatic Fever and Rheumatic Heart Disease

T. Duckett Jones, M.D.

The treatment of rheumatic fever and rheumatic heart disease offers many difficulties. As indicated by the previous discussers, there is no positive diagnostic test for this disease, and it is difficult to determine when the active stage of the disease comes to an end. No specific therapy is available at present. Both the recurring and frequently progressive nature of the disease add further disadvantages. When confronted with a child or young adult with definite rheumatic heart disease, the medical profession is presented with a distinct challenge. All too often both the private and clinic physician fail to accept this challenge. Following arrangement for the care of the obviously ill patient, interest often lags, and little may be done to aid the young individual in the chronic battle which he is to wage. It is important that we fully appreciate the chronicity of rheumatic fever, familiarize ourselves with the signs and symptoms of the active disease, and evaluate these at each visit rather than merely determine the often academic question of the evaluation of heart murmurs. Much of the battle against tuberculosis was won by a large group of physicians learning the life cycle of the disease by long observation of patients in sanatoria. In this country we are yet to organize programs on a broad scale to insure the proper care of the rheumatic subject. England has fostered much of the pioneer work. The city of London expends over one million dollars annually in the chronic hospital care of rheumatic fever subjects and offers some

1,100 beds for such service. This is in addition to beds available for the acutely ill in general or children's hospitals. Better facilities for both the care and the study of patients with rheumatic fever will doubtless be made available when the results of long follow-up studies are concluded. Some of the varied aspects of treatment will be briefly discussed.

The Acute Illness.—The patient acutely ill with rheumatic fever is best treated in hospitals where good medical and nursing care are available. The economic status of the majority of the patients often makes hospital care necessary. It is especially advisable when any degree of heart failure is present. The measures of value during the acute illness, well known to members of the medical profession, consist of absolute rest, forcing fluids (save in the presence of edema), sedatives, salicylates, digitalis, and diuretics. Salicylates are almost universally used during this stage of the illness, although the results are often discouraging. All rheumatic fever patients do not respond to salicylate therapy, and I know of no investigations which prove conclusively that salicylates in any way alter the degree of heart disease which the patient develops. This drug unquestionably makes the patient more comfortable and helps with the exudative phenomena of the disease. Hence, during the acute illness salicylates are of value.

In recent years the English observers have pointed out that salicylates will often prevent recurrences of rheumatic fever. They suggest giving moderately large doses of salicylates to each rheumatic subject at the time of a respiratory infection, the drug to be continued for a considerable period of time. In our experience salicylates mask the symptoms of rheumatic fever and give the physician a false sense of security. Whether salicylate therapy prevents recurrences is distinctly open to question, and as yet far from proved. It would seem satisfactory to use salicylates whenever necessary for the comfort of the patient and to withdraw them when no longer necessary for this purpose.

The use of digitalis at the time of congestive heart failure is of debatable value. Many conflicting reports are to be found in the literature. Infection is present at the time of failure and interferes with a completely satisfactory response to digitalis therapy. The patient requires larger doses than ordinarily necessary for digitalization in an infection-free patient. It is relatively simple to add the burden of digitalis toxicity to an already ill patient, and the drug, if used, should be given with caution. In a patient with very active rheumatic fever it is often impossible to lower the pulse rate with this drug. The good result of digitalis therapy at times may be more properly ascribed to the diuretic effect of the drug than to its direct effect upon the heart.

In recent years diuretics have assumed a more prominent role in the treatment of patients with heart failure, and this would seem to be especially true of the patient with rheumatic heart disease. It is often possible to keep the patient edema-free by the use of such mild diuretics as those of the xanthin group. In more obstinate cases, mercurial diuretics have been found to be satisfactory, being given either as a suppository or intravenously. In the presence of frank edema it is, of course, necessary to limit the fluid intake of the patient. Save for the questionable value of digitalis, the patient with congestive failure as the result of rheumatic fever and rheumatic heart disease should be treated much as patients with heart failure from any cause.

Save for the monocyclic form of rheumatic fever, which rarely occurs in children, rheumatic fever is a chronic disease punctuated by cycles or more definite recrudescences, and the period of illness may last from a few months to several years. The need of the general hospital bed for the acutely ill and for short-stay diagnostic problems, usually limits the stay of the rheumatic fever patient in such an institution to a comparatively short time. Exposure of the patient to infections, especially those of the respiratory tract, makes the ward of the general hospital an

unwise place for the rheumatic child to remain long. Other arrangements must be made as the patient improves.

Care of the Chronic Phase.—Signs and symptoms of rheumatic fever may continue almost indefinitely. Laboratory studies present evidence of active rheumatic fever even after the clinical evidence of the disease subsides. As one studies the disease, the impression grows stronger that it is active rheumatic fever (even subclinical) that is the important feature of the disease. Rheumatic fever is the cause of death in the fatal cases and is responsible for varying degrees of heart disease in those spared. Long bed rest would seem just as advisable in this disease as in tuberculosis. It is available in only a few institutions in this country as yet. No actual statistics are available which prove the value of such long bed care, but some of the obvious advantages may be mentioned.

1. Following the acute illness, mild symptoms may continue for long periods.
2. Even after the disappearance of the clinical, or obvious, symptoms, laboratory tests usually show a continuation of the activity of rheumatic fever, and at this time recurring attacks are frequent.
3. Rheumatic heart disease may develop or increase as long as active rheumatic fever continues.
4. Continued rest in bed allows the body to conserve its entire energy for the fight against the disease.

Other general and important features most easily available while receiving long bed rest are:

Protection against exposure to cholds and sore throats.

Freedom from emotional or family difficulties.

A well balanced diet.

Ultraviolet light treatment.

Education of the patient and family concerning the disease.

A good psychological attitude of the patient to his limitations.

The maintenance of regular scholastic standing by bedside instruction.

Vocational guidance and occupational handicrafts.

Convalescent or Foster Home Care.—When all evidence of active rheumatic fever subsides (normal laboratory studies as well as the absence of clinical symptoms), the actual rehabilitation of the patient may be said to begin. It is helpful and important that the child return to a moderately active life in good surroundings and under careful supervision. During this period, improvement is usually rapid and from a few weeks to months of carefully observed activity as well as protection from respiratory infection may be of tremendous importance in his future health. In each instance the degree of permanent heart damage must determine the physical activity of the individual patient. In general, relatively few young rheumatic fever subjects have a sufficient degree of heart damage to warrant extreme restriction, although it would not be feasible to return them to an active physical life too rapidly.

Our general rule has been to see that they have an abundance of rest with a long rest period after lunch for some months after the disease becomes inactive. In addition, an attempt should be made to maintain their scholastic standing during this period of convalescence, since we have not allowed the rheumatic fever subject to return to full-time public school activity for at least six or eight months after his disease has become quiescent. The results of such restriction have on the whole proved satisfactory.

Advice During Quiescence.—At this period an attempt should be made to increase the patient's general resistance. The home conditions should be bettered wherever possible, and the family urged to see that the child has a separate bed, if not a separate bedroom. We have found this to decrease the number of respiratory infections.

In a carefully followed group of some 750 rheumatic fever subjects, colds or sore throats were the obvious precipitants of recurrent rheumatic fever in 60 per cent of the observed instances. This makes respiratory infection the most important single factor in the life history of the disease. The prevention of respiratory infection is an almost impossible task, and we have not been impressed with the value of vaccine therapy. However, the avoidance of crowds, the cooperation of the school authorities in attempting to prevent exposure to respiratory infection, and at times the isolation of other members of the family with respiratory infection will do much to curtail this factor. Should respiratory infection occur in the patient, he should spend several days in bed.

It is well to see that a well-balanced diet is available. It is difficult in poorer patients to be certain that the patient receives a quart of milk daily. We have insisted that each child receive the juice of at least one orange daily, and as a rather routine measure have used some form of vitamin D during the winter months. The patient and parents should be well informed of the recurring and chronic nature of rheumatic fever, and any symptomatology reported immediately to the clinic or private physician.

Especially important is it that the patient should pay frequent visits to the agency controlling his medical care. During the early years of the disease process this should be as frequent as every three or four months, oftener if there is any question of active rheumatic fever. Should the patient do well for five or six years, it is then feasible to decrease the visits to every five or six months. This becomes fairly important when one appreciates that in a group of 348 carefully observed patients having 771 recurrences, approximately 80 per cent of the recurrences were noted during the first five years of the disease.

Foci of Infection.—Since the etiology of rheumatic fever is closely associated with streptococcus infection, the removal of foci of infection, especially tonsils, has been a major feature of the treatment of the disease. There is at present no distinct agreement concerning the value of such a procedure. Many of our patients have had a tonsillectomy performed prior to the onset, and we have not been impressed with the value of tonsillectomy in altering the course of the disease. It is not possible to denude the pharynx of all lymphoid tissue, and we have not seen tremendous diminution in the number of respiratory infections following tonsillectomy, though their severity would seem to be somewhat lessened. It has previously been suggested that tonsillectomy be performed during the height of rheumatic fever, but this practice has been discarded. It would seem wise to determine the question of such an operative procedure in the individual patient, tonsillectomy being favored in a patient with a history of very frequent sore throats. Once this procedure has been decided upon, it should be performed only in the absence of clinical and laboratory evidence of active rheumatic fever. In this way many recurrences of rheumatic fever will be avoided. Extraction of teeth should also, if possible, be carried out in the absence of active rheumatic fever. We have observed fatal recurrent rheumatic fever following such a procedure.

Special Procedures.—Many therapeutic agents have been suggested in treating rheumatic fever and rheumatic heart disease subjects, but their use has proved of questionable value. So far as is known, no therapy involving the use of streptococcus vaccines or antisera has resulted in unqualified success. Convalescent serum has also been tried. Some have advocated frequent small transfusions. Splenectomy has been performed without success. The use of nonspecific protein shock therapy and hyperthermia has more recently proved of value in a limited series. This latter type of therapy would seem much more applicable in the treatment of chorea, although the relatively benign nature of chorea must be remembered. Violent, exhaustive chorea is uncommon today, and to submit patients with rather mild choreiform movements to such stirring therapy would seem rarely indicated.

Sulfanilamide has proven to be valueless and even dangerous. Deep x-ray therapy and high vitamin C diets have been advocated by some workers. There has been much interest in transportation of the rheumatic to a subtropical climate, but even this has failed to be a panacea.

With our present lack of knowledge concerning the etiology of rheumatic fever, the discovery of any specific therapeutic agents would seem to be largely a matter of chance.

Prognosis.—Factors influencing the prognosis in rheumatic fever are little understood. We have no measure at present of host resistance. To a considerable extent the outcome of rheumatic fever is dependent upon the fulminance of the individual attacks of rheumatic fever. The age of onset does not seem to be as important as previously considered. The majority of children who develop conspicuous heart enlargement early in the course of their disease, have a relatively poor outlook and, if they survive the first five or six years of the disease, will usually have a definite limitation of physical activity and die not later than middle life.

Results of Ten Years' Observation of 1,000 Rheumatic Fever Subjects.—We have been interested in obtaining data on the results which can be obtained by careful study and observation of rheumatic fever subjects who have been given prolonged bed care during active rheumatic fever. One thousand such patients have been observed at the House of the Good Samaritan since 1921 and followed for ten years. There are both discouraging and encouraging features. At the time of original discharge from the hospital, 672 of the 1,000 patients on examination had evidence of some degree of rheumatic heart disease, while 328 had no clinical evidence of rheumatic heart disease. Of the patients without evident heart disease, 71 (22 per cent) developed subsequent rheumatic heart disease. One-half of these developed heart disease without evident rheumatic fever. The large majority, 251 (76 per cent), continue to show no evidence of rheumatic heart disease ten years after the onset of their disease.

Of the 672 patients with rheumatic heart disease, 230 (34 per cent) have died of their disease. In 188 (28 per cent) the heart disease status is unchanged. In 120 (18 per cent) there has been a progression of heart disease, whereas in 119 (18 per cent) there has been a distinct improvement in the heart disease. In over one-half of the latter group, clinical evidence of heart disease has disappeared, and in the remainder there has been a distinct regression of physical signs. On 15 of these patients we have no reliable recent information. It is interesting in summarizing the present status of the entire group that 242 are dead. This mortality of 24 per cent places rheumatic fever as one of the severe diseases of early life. The majority of these patients died of rheumatic fever, congestive heart failure being present in a large majority. The average age at death was 13 years. Sixty-eight per cent died within the first six years of their disease. At the present time, 310 (31 per cent) have no clinically demonstrable heart disease and are leading normal lives. Four hundred and twenty-seven (43 per cent) have definite heart disease on examination, but the majority of these (287) have no limitation of their physical activity. This means that 59.7 per cent of the entire 1000 are living at the present time and have no limitation of their physical activity. Fourteen per cent have moderate to marked limitation of physical activity and proceed to the second decade of their disease with a poor prognosis. This group represents rheumatic heart disease as seen in the adult wards of the general hospital and medical clinic. In 21 no reliable information is available. Despite the high mortality, the finding of normal physical life in 60 per cent of such a large group at the end of ten years is heartening and warrants continued attempts to see that these patients have the best possible medical observation and care.

Recently Schlesinger has reported a somewhat similar group, although his 1,000 patients have not been followed for a period comparable to ours. The findings of Schlesinger, as well as the results in our own series, indicate that the long-time care and observation of patients with rheumatic fever and rheumatic heart disease is a worth-while undertaking. Despite our lack of etiological knowledge concerning rheumatic fever, much can be accomplished with these patients.

No attempt has been made to cover all pertinent features relative to treatment. It is hoped that these three summaries will stimulate a free discussion of the many factors involved.

Diagnosis of Rheumatic Fever

M. J. Shapiro, M.D.*

Until the etiology is discovered, it will be necessary to make the diagnosis of rheumatic fever on the clinical picture. The rheumatic infection is characteristically variable in its manifestations; yet a correct diagnosis can be made in the great majority of instances if the disease is well understood. In recent years several methods have been introduced to assist in making a diagnosis of rheumatic fever. These include a number of complicated laboratory procedures, skin tests, throat and blood cultures, the artificial production of rheumatic nodules, etc., but none of them has proved of practical value. It is necessary to understand well the clinical signs and symptoms of the rheumatic state in order to make an early diagnosis. One of the most important facts that has come out of the vast amount of research done on this disease in recent years, is that rheumatic fever is essentially a chronic, long-continued infection. The comparison of rheumatic fever with tuberculosis and syphilis is well taken. To understand the rheumatic state thoroughly, one must be impressed with its chronicity. We speak of repeated attacks of rheumatic fever each spring and fall for a number of years. Actually, in most instances, this is the same attack with exacerbations. Frequently, patients are seen who become infected with rheumatism and continue to show evidence of low grade infection for months and years; gradually the heart becomes involved, and the patient may expire with active carditis and every evidence of rheumatic activity.

Incidence.—Rheumatic fever occurs most commonly in the temperate zones. It is relatively rare in the tropics as well as in the arctic regions. As is well known, it occurs most commonly in the lower economic groups and is distinctly a familial disease. It occurs most commonly in the early spring and late fall and is relatively uncommon in the middle of the summer and during the cold winter months. Rheumatic fever becomes prevalent during epidemics of upper respiratory infections and is prone to occur when scarlet fever is prevalent. Many cases of rheumatic fever develop immediately after scarlet fever, and there seems to be some definite relationship between these two diseases.

It is primarily a disease of early childhood, and it occurs most frequently between the ages of 5 and 8 years. It is about equally distributed in both sexes and is common in all racial groups. There seems to be no correlation between the number of attacks and the extent of cardiac damage. In my own experience, a number of patients with marked cardiac involvement have had only a single attack of rheumatic fever; yet other children who had had several attacks escaped with no cardiac damage. The earlier the onset of the disease, the more likely is the heart to be attacked; and the more severe the attack of rheumatic fever, the more involvement in the heart. It has been stated that practically every patient with rheumatic fever shows some cardiac involvement and that 60 per cent of such patients will eventually develop permanent damage of the heart. This is especially true in children.

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In studying the histories of our patients with well-developed rheumatic heart disease, I found that they gave a positive history of rheumatic infection in practically every instance. Recently, in analyzing 100 of such histories, I found that 60 per cent of the patients had acute polyarthritis; 8 per cent, chorea; while 16 per cent had both acute polyarthritis and chorea; 10 per cent had subacute polyarthritis; 4 per cent, primary carditis; while 2 per cent gave no history of rheumatic infection of any kind. Thus a positive rheumatic history was obtained in 98 per cent of these patients.

In the typical case with joint involvement, diagnosis is not difficult. The joints become stiff, painful, and red, and the process jumps from one joint to another. The child is bedridden with fever and toxemia, and the diagnosis is apparent. In a smaller group, however, the polyarthritis may be so mild that the child may limp about but may never go to bed, and the diagnosis is easily missed for some time. Such patients often have slight swelling and local heat of various joints which is overlooked by the parents. If examined carefully, the children will often be found to have low-grade fever. Patients with these symptoms need to be differentiated from normal children who complain simply of leg pains. In a number of recent articles on rheumatic fever, patients with so-called growing pains have been considered as rheumatic patients. As has been stated, a small group of patients with rheumatic fever have mild joint symptoms. However, the great majority of children who complain of leg pains are not suffering from rheumatic fever. At times it is difficult to differentiate these two groups of patients. As a result of a number of years of experience with this problem, I have worked out the following differen-

TABLE I

DIFFERENCES BETWEEN NONRHEUMATIC "GROWING PAINS" AND JOINT PAINS OF SUBACUTE RHEUMATIC FEVER

	NONRHEUMATIC "GROWING PAINS"	JOINT PAINS OF SUBACUTE RHEUMATIC FEVER
Age at onset	Early childhood—often continues through adolescence.	Most commonly between 6 and 7 years of age—often occurs in attacks following upper respiratory infections or other infectious diseases.
Time of pain	At end of day—especially during night often awakening the child several times. Pain is gone in the morning and usually does not occur during the day.	On first getting out of bed in the morning—during entire day—especially on motion; often causing limp. Patient feels better on getting warm in bed.
Location of pain	Most commonly in muscles of legs and thighs—rarely in muscles of upper extremities. Occasionally involves knee joints.	In joints, themselves, of upper and lower extremities.
Other signs of rheumatic activity	Usually none.	Repeated bouts of joint pains; nosebleeds, characteristic skin rash; pallor, fever, etc.
Objective signs in joints	None.	Joints often have slight increased local heat and mild swelling usually overlooked by patient and parent.
Family history of rheumatic fever	Uncommon.	Common.
Laboratory findings	Normal sedimentation rate. Normal leucocyte count. Normal hemoglobin.	Increased sedimentation rate. Mild increase in leucocyte count. Moderately decreased hemoglobin.

tial diagnostic chart which should assist in separating children with subacute rheumatic fever from normal children who complain of leg pains (Table I). Among the diagnostic clinical signs which occur most commonly with the polyarthritis of rheumatic fever are the rheumatic nodule and certain skin manifestations. The *rheumatic nodule* is almost pathognomonic of rheumatic fever. The incidence of these nodules varies in different parts of the world. In England they are quite common. They are also fairly common along the eastern coast of the United States but in the Middle West and Far West, they are quite rare. In our clinic I have seen rheumatic nodules most commonly in those patients who had serious rheumatic disease and in whom the prognosis was not good. The nodules are usually small, about the size of a grain of wheat, but they may be considerably larger. They commonly occur in crops and appear to be attached to the joint tissues or periosteum, but the skin over them moves freely. They are usually quite hard and not particularly tender. They are most often found over the elbows, knuckles, wrists, knees, scalp, and under the skin over the vertebral column. The nodules may be present for only a few days but may persist for weeks.

The *skin rash* of rheumatic fever occurs most often in association with polyarthritis. Erythema marginatum may be considered almost pathognomonic of rheumatic fever. This is a most interesting skin condition. It may appear and disappear several times in the same day. It occurs over the entire body but most commonly over the chest and abdomen. It is characterized by circular serpiginous lesions with a pale center and a fine threadlike, slightly raised, reddish border. As has been stated, the rash is extremely evanescent. It is considered significant of rheumatic activity; yet I have known patients who have continued to have erythema marginatum for many weeks and months with no other evidence of rheumatic activity, even with a normal sedimentation rate. Erythema multiforme is common in children with rheumatic fever. It can occur suddenly over the entire body, and in some instances a differential diagnosis may be difficult. The rash may be widespread and simulate measles. Urticaria is not common. In one patient in our convalescent ward at the present time, rheumatic nodules appear in crops and with each crop of nodules an additional patch of urticaria appears over the skin. Urticaria may occur over the entire body. In spite of what has been written to the contrary, erythema nodosum, in my experience, is unusually rare. I can remember only one instance in which erythema nodosum occurred during an attack of rheumatic fever. I have seen one case in which purpura was a complicating factor in an otherwise relatively mild attack of rheumatic fever. Psoriasis has been mentioned in relation to rheumatic fever, but I have not seen it. It most commonly occurs in connection with chronic atrophic arthritis.

Spontaneous severe nosebleeds often accompany rheumatic infection. Epistaxis is usually a sign of continued rheumatic activity. The usual blood examination is not characteristic in rheumatic fever. However, the sedimentation rate of the red blood cells is of extreme value both in diagnosis and in judging the activity of the infection. The sedimentation rate is used in all clinics and hospitals where rheumatic fever is treated. It is a simple test and can be done in any office. Children with rheumatic infection will invariably show an increased sedimentation rate.

Chorea.—Chorea has long been considered a major manifestation of the rheumatic state. In the last few years, however, some studies have appeared which tend to cast doubt on the rheumatic background of chorea. It has been demonstrated that choreic patients usually do not show evidence of chronic infection. They have no fever and the sedimentation rate is usually normal. According to these writers, chorea alone rarely causes rheumatic endocarditis, it is only when polyarthritis occurs in association with chorea that the heart becomes involved. The majority of in-

vestigators are not altogether in accord with this point of view. Most of them still believe that chorea is rheumatic in origin and that it is an important cause of rheumatic heart disease.

Chorea occurs most frequently during the adolescent period; it is five times more common in girls. It may follow immediately after an emotional upset. Acute polyarthritis and chorea rarely occur at the same time but more frequently alternate in occurrence. In the typical case the diagnosis is not difficult. The characteristic muscular incoordination is diagnostic. Chorea may involve only half of the body and appear as hemichorea. In some of these cases, there is a pseudoparalysis of flaccid nature, and the patient may drag an arm and leg simulating hemiplegia. The heart is usually moderately involved; the endocarditis develops gradually. In most instances, the condition clears up in a few months, but chorea may persist in a mild form for years. It is sometimes difficult to differentiate chorea from the early muscular incoordination of encephalitis. Patients with early chorea sometimes attend school for weeks, having more and more difficulty in writing, sewing, and gymnasium, before the condition is recognized. It would be well if all teachers and school nurses could see a case of active chorea. They could help in making an early diagnosis.

Carditis.—In another small group of patients, the rheumatic infection manifests itself as a primary carditis. Such patients often complain of fatigue. They have a low-grade fever, usually develop a pallor, and the diagnosis may be in doubt for some time. The onset may be quite sudden and severe, with high fever and prostration, and the diagnosis will not be clear until the signs of endocarditis become apparent. In most of these patients, the onset is gradual, and the diagnosis becomes definite when the heart condition is detected. The signs of infection may continue for many weeks before the endocarditis is developed enough so that a diagnosis can be made. In any child with an unexplained low-grade fever, the diagnosis of primary rheumatic carditis should be considered.

Development of Rheumatic Heart Disease.—Rheumatic heart disease is not a complication of rheumatic fever, but it is part of the disease. The cardiac involvement may be acute and severe from the very outset, causing a pancarditis with pericardial effusion, followed by early death due to toxemia. Fortunately, the cardiac involvement is more often gradual in nature. A systolic murmur may appear early in the process and suggest mitral disease. However, it is not uncommon for such murmurs to disappear after the acute condition recedes. A positive diagnosis cannot be made until many months have elapsed; the heart may escape damage entirely, but, even when the systolic murmur disappears for a time, one may be surprised to find a well-developed mitral stenosis in such a patient a year or two later. The first sign of aortic regurgitation is the distant blowing diastolic murmur heard along the left border of the sternum. This murmur is missed more often than any other. Some men seem to be unable to hear the diastolic murmur. This murmur may appear and disappear from time to time until it finally becomes constant. At this time, the peripheral circulatory findings may be entirely normal, and the characteristic Corrigan's pulse and blood pressure changes may not appear for many months.

The electrocardiogram has been used experimentally to demonstrate myocardial involvement in rheumatic fever. Electrocardiography is of value in a hospital where research is being carried on in rheumatic fever. However, the information obtained from electrocardiography in the usual case is of so little practical value that I do not believe tracings are necessary in the individual patients treated by the private physician. Much more important is the x-ray examination. Early in the onset of rheumatic heart disease the x-ray films may show the heart normal in size and contour, but it will not be long before some evidence of change either in contour or size develops. There has been considerable research carried on in x-ray of the

heart. Much stress has been placed on the inaccuracy of the usual cardiothoracic measurements. Many workers believe that the earliest signs of cardiac involvement may be detected much more efficiently with the aid of the fluoroscope. I am inclined to agree with this point of view, but it is my impression that many mistakes will be made as it is often difficult to determine when the heart is or is not slightly enlarged. If the x-ray examination will be used properly, that is, as only one part of the physical examination and coordinated with other clinical and laboratory findings, mistakes will be fewer.

Conclusions

There is no known diagnostic laboratory test for rheumatic fever. The diagnosis must still be based on the clinical picture. Rheumatic fever is characteristically a chronic low-grade infection. It manifests itself most commonly as an acute polyarthritis or chorea. It may, however, appear as a subacute polyarthritis which must be differentiated from nonrheumatic leg pains. In a small percentage of patients, the condition appears as a primary carditis. The rheumatic nodule and erythema marginatum are pathognomonic of rheumatic infection. Cardiac involvement is usually slowly progressive and can be detected by careful auscultation from time to time and by repeated x-ray studies. The sedimentation rate of the red blood cells is a useful diagnostic procedure in rheumatic fever.

Symptoms and Signs of Rheumatic Fever

Robert L. King, M.D.

In the more recent and broader conception of rheumatic fever, the clinical signs and laboratory findings must be considered in relation to systemic and usually chronic disease rather than the historical acute inflammatory disease of the heart and joints. Its manifestations are protean and are subject to a wide variation in onset, duration, and degree of severity.

Swift[1] has outlined several descriptive clinical types of rheumatic fever—monocyclic, polycyclic, and continuous. In the monocyclic type there is a sudden onset of symptoms including a rising fever, migratory polyarthritis, pancarditis, severe toxemia, and drenching sweats. These symptoms reach a climax in six to ten days and subside in two weeks, although there may be a low-grade fever to the end of the third week. In the majority of instances the first cycle does not complete the picture, but instead the patient enters another bout of fever, with some other manifestations, thus progressing to the polycyclic type. Repeated recrudescences with an interim of relatively mild symptoms and signs may continue over a period of months or years. The clinical picture of the disease may be neither that of the simple monocyclic nor that of the polycyclic variety but may assume the continuous form wherein the fever and clinical signs are irregularly sustained. Most attacks of rheumatic fever last three to four months, and the more chronic forms may last for as long as five to six years. Swift[1] has emphasized the false sense of security that may be felt after the administration of salicylates. These reduce the fever and alleviate the joint pains, which may lead to the withdrawal of precautions while the disease progresses. Many have recurrences only in the first five or six years of the disease, while the progressive cases have recurrences at almost any period.

The severity of rheumatic fever varies from the severe type, in which the patients are dangerously ill, the clinical manifestations prominent and the laboratory tests definitely abnormal to the low-grade type in which patients do not appear ill, the clinical signs are mild, and laboratory tests occasionally normal. Furthermore, in the relatively recent past we have come to recognize the subclinical type, in which, after clinical signs of rheumatic fever have subsided (occasionally from the onset)

there may be only laboratory evidence of the activity of the disease. The significance of this type cannot be overemphasized on account of the imperative need of properly supervised precautions necessary in an attempt to prevent further cardiac damage. The laboratory findings usually return to normal within six months after the subsidence of clinical manifestations. The most important abnormal findings are an elevated leucocyte count (over 10,000) or increased sedimentation rate, or both. Persistently abnormal laboratory findings which are otherwise unexplained indicate persistently active rheumatic fever.

Clinical Signs

Massell and Jones,[2] in an analysis of 121 hospital admissions of patients with rheumatic fever, found clinical as well as laboratory evidence of active disease in 60 per cent of the instances, while 40 per cent had only laboratory evidence. In rheumatic fever the clinical signs most frequently observed are fever, nodules, chorea, epistaxis, joint pains, precordial pain, rash, congestive failure, abdominal pain, pneumonitis, pericarditis, and pleurisy.

Fever.—A persistent or frequently intermittent rectal temperature of 100° F. or more is one of the most frequent manifestations of active rheumatic fever. Usually the fever parallels the activity of the disease and other manifestations. The fever is not ordinarily sustained except occasionally at the onset or in severe attacks. The tendency is toward daily elevations of 100-101° F. for a time and then cycles characterized by bouts of fever after a temperature normal or nearly so for days or weeks. After the subsidence of other clinical signs a low-grade fever may remain for many months as the only clinical sign of activity. Careful recording of the daily rectal temperature during convalescence and in suspicious cases cannot be overemphasized.

Subcutaneous Nodules.—The incidence with which subcutaneous nodules occur in rheumatic fever has been reported with considerable variation. They are regarded by many authorities as representing the characteristic pathology of rheumatic fever. It is generally agreed that they represent proliferative changes and most often occur in patients with severe heart disease. Their occasional presence with the milder types of infection is noteworthy, and therefore it does not always warrant a grave prognosis. They appear in crops as movable painless nodules of variable size and consistence, on bony prominences and tendons. Just as their presence indicates active disease, so their disappearance is associated with improvement. They rarely exist in the absence of other clinical manifestations; however, when they do they should be considered as evidence of activity for the period of their existence, which may be from a few days to several months.

Chorea.—Sydenham's chorea has long been considered a manifestation of active rheumatic fever. Tics and other purposeless movements not truly choreiform should not be considered as of rheumatic origin. Ash and Einhorn[3] have recently expressed the opinion that any child with chorea should be considered as potentially rheumatic. Bland and Jones,[4] in their review of 1,000 rheumatic fever patients, showed that of 134 patients who had chorea alone only 3 per cent had rheumatic heart disease. They believe that, although chorea is a manifestation of rheumatic fever, in the absence of other clinical and laboratory evidence it indicates a mild form of the disease.

Epistaxis.—Repeated epistaxis in a rheumatic fever subject should arouse suspicion of activity. Coburn[5] found that it precedes recrudescences of the disease more often than any other symptom, and that it often accompanies active rheumatic fever.

Joint Pains.—The arthritic manifestations, while often subjectively prominent and diagnostically important, are not otherwise particularly significant features of the disease. In children joint symptoms are fleeting and rarely significant. They

usually occur with the first or second attack and often never again. The migratory polyarthritis characterized by swelling and redness and pain is a more pronounced feature in adults than in children. In a rheumatic subject the existence of any arthritic symptoms should arouse suspicion of activity. Jones and Bland,[4] in their review of 1000 patients, found that 70 per cent had at some time had joint symptoms.

Erythemas.—Erythemas in a rheumatic fever subject are recognized as a manifestation of activity of the disease. They are most frequently observed after the acute phase and appear to be associated with subsiding activity. Erythema multiforme is the most common, in the form of erythema marginatum and less often nodosum or papulatum. Erythema marginatum occurs as pale red or bluish red ringlets with pale centers. It is most often found on the flexor surfaces of the arms and on the chest, rarely on the legs, and never on the face or mucosae. The rash is evanescent, usually disappearing in eighteen to twenty-four hours, but likely to recur in a day or two. It may be the only clinical evidence of activity and may occur even with normal laboratory data.

Cardiac Signs.—Neither the severity of the rheumatic fever nor the degree of fever bears any constant relationship to the accompanying cardiac involvement. The development of murmurs in the absence of typical symptoms and signs may suffice to confirm the diagnosis of rheumatic fever. Cardiac involvement is the most important feature of the disease. The patient may escape evident carditis in the initial attack of rheumatic fever, but seldom is he so fortunate a second time. Carditis appears in a more serious and progressive form in young patients, while in older patients polyarthritis is more pronounced.

Precordial pain is a frequent symptom of active rheumatic fever. Severe pain is usually attributed to pericarditis accompanying severe carditis in the early or acute stages of the disease. More commonly the pain is transitory and mild. The cause of this is not well understood—it is probable that pleuritis or "silent" pericarditis plays a part in its production. Anginal pain in severe rheumatic fever has been reported, with the suggestion that it may be due to coronary disease of rheumatic origin.

With rheumatic activity there is a tendency for the pulse rate to be persistently high. This sign alone, however, is unreliable on account of the extracardiac influences, most often of neurogenic origin. In order to evaluate this sign properly, careful recording of the pulse with the patient sleeping is important, especially in the absence of other clinical and laboratory evidence of rheumatic fever.

The presence of congestive failure or the onset of auricular fibrillation indicates further myocardial damage and should be considered as strong evidence of active disease in a rheumatic fever subject under 30 to 40 years of age.

The development of murmurs in rheumatic carditis depends upon the degree of insufficiency or stenosis created and on the state of myocardial efficiency. Significant variations of murmurs are usually noted over a period of months or years; however, transient murmurs may occur with fulminant rheumatic fever or acute dilatation.

Abdominal Pain.—Abdominal pain frequently occurs in patients with rheumatic fever. Coburn[5] found it to occur second in frequency only to epistaxis. The severity is variable, and it may simulate appendicitis, thus creating an important problem in differential diagnosis. The cause of abdominal pain, though admittedly unknown, has been thought possibly to be rheumatic disease of the mesenteric or other arteries. Keith[6] recently suggested that abdominal pain, as well as nausea and vomiting, may be due to overstimulation of the vagus. While these symptoms usually occur with other manifestations, their presence in a known rheumatic subject must be regarded with suspicion and provoke a search for other evidences of activity.

Loss of Weight.—The constitutional effect of infection in rheumatic fever produces a loss of body weight commensurate with the severity and duration. A steady and appreciable gain in weight is usually not manifest until activity subsides. In a rheumatic fever patient, an unexplained failure to gain weight may be indicative of continued activity. Therefore, as an index to the progress of the disease, weight records are of considerable value.

Pleuritis and Pneumonitis.—During the course of rheumatic fever, and often occurring with exacerbation of the disease, transitory pleural pain may be present, and a friction rub may be heard. This may or may not accompany pneumonitis with frank lobular consolidation. Physical signs are often not typical of consolidation, although the extent of the lesion may be clearly shown on the roentgenogram. Pleuritis during the course of rheumatic fever is generally regarded as of rheumatic origin, but a similar explanation of pneumonitis has not been universally accepted.

Laboratory Findings

Leucocyte Count.—An elevation of the leucocyte count usually accompanies active rheumatic fever and is known frequently to persist after clinical evidence has disappeared. In the acute phases of the disease, the white cell count generally ranges from 12,000 to 16,000. Elevations of 20,000 to 30,000 may occur in the more fulminant forms of the disease. The count diminishes with the disappearance of other manifestations; however, a count of 10,000 or more may persist for months afterwards. The diurnal and other widely recognized variations must be kept in mind. For the most informative data, counts should always be made at the same time of the day. The Schilling count typically shows a shift to the left. However, the relative number of immature cells of the myelocytic series is not considered as reliable as the leucocyte count. A definitely elevated leucocyte count in a rheumatic subject following clinical manifestations or in the absence of them is adequate evidence of activity.

Sedimentation Rate.—The sedimentation rate of blood to which an anticoagulant has been added is known to be increased in many diseases. In active rheumatic fever the rate usually shows a definite increase over normal, and this increase may persist for weeks or months after the disappearance of clinical signs. A persistently elevated rate in the absence of congestive failure, respiratory infections, or operative procedures is considered indicative of active disease. Struthers and Bacal[7, 8] found that the rate is increased in rheumatic fever and that the return to normal is slower when carditis exists. Furthermore, they found that chorea without carditis was accompanied by a normal sedimentation rate and normal leucocyte count. If the albumin-globulin ratio is altered, as when congestive failure is present, the sedimentation rate may be low or normal. The Rourke and Ernstene[9] method seems to be preferred by most workers. The maximum normal rate per minute for this method is 0.38 mm. Correction for anemia should be made for accurate interpretations. In view of the fact that the sedimentation rate is less subject to daily fluctuations and other influences than the leucocyte count and because the deviations from normal are more pronounced, the sedimentation rate is considered the most valuable single blood study in rheumatic fever.

Anemia.—It is well known that secondary anemia accompanies active rheumatic fever. Its intensity varies with the degree of activity; the frequency, number, and severity of the cycles experienced; and the total duration of the active phase. Since improvement in the blood picture parallels other clinical and laboratory evidence of the disease, such a finding may be interpreted in corroboration of other signs.

Urinary Findings.—That nephritis should be considered as a part of the rheumatic fever syndrome has not been generally agreed upon. In the acute phases albuminuria, hematuria, cylindruria, and altered renal function are often noted. With improvement in the disease these findings diminish and leave the kidneys free from signifi-

cant impairment of function. The finding of red blood cells in the urine in the relatively quiescent phases may furnish collateral information as to the progress of the disease.

Electrocardiographic Changes.—Disturbances of conduction graphically shown by the electrocardiogram are frequently observed in rheumatic fever. Transient abnormalities of the QRS complex and S-T interval, inversion of the T-wave, and prolongation of P-R have been reported. During the course of rheumatic fever, prolongation of the P-R interval, which is the most helpful sign of carditis, may exist for as long as two years. Permanent changes in auriculoventricular conduction from rheumatic fever, although reported, are rare. Keith[6] recently presented evidence to show that overstimulation of the vagus in acute rheumatic fever accounted for those disturbances rather than the actual involvement of the conduction tissues by the disease process and suggests that informative diagnostic data may be obtained by frequent electrocardiographic tracings after the administration of atropine.

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DISCUSSION

DR. J. J. MILLER (SAN FRANCISCO, CALIF.).—What is the present concept of the etiological agent of rheumatic fever with particular reference to the status of the hemolytic streptococcus vs. a virus as the causative agent?

CHAIRMAN JONES.—I am sure that you are all familiar with the work of Dr. A. F. Coburn at the Presbyterian Hospital in New York. Dr. Coburn has presented abundant evidence of the close association between the clinical picture of rheumatic fever and the development of immune bodies indicative of hemolytic streptococcus infections. He feels that the latter are necessary to the development of the clinical picture of rheumatic fever. In Boston we have carried out extensive studies concerning this relationship. As previously mentioned, in a large group of rheumatic fever subjects, 60 per cent of the observed recurrences were associated with a preceding cold or sore throat. However, other events, seemingly nonstreptococcal, have been observed to precipitate clinical recurrences of rheumatic fever. In analyzing our rheumatic fever material regarding the disease and the development of hemolytic streptococcal immune bodies, we have found the following: hemolytic streptococcus immune bodies (especially antistreptolysin) are found in patients with their first attack of rheumatic fever in as high a percentage as develop in scarlet fever and known streptococcus diseases. In rheumatic subjects without active rheumatic fever hemolytic streptococcus immune bodies develop in approximately two-thirds after an attack, regardless of whether rheumatic fever recurs or not. Hence, while the majority of rheumatic fever recurrences are associated with the presence in the blood of hemolytic steptococcus immune bodies, the disease does occur without the development of such immune bodies, and the same immune bodies are frequently present in rheumatic subjects without subsequent active rheumatic fever. Further, in patients with active rheumatic fever, hemolytic streptococcus immune bodies may develop following an attack, regardless of whether or not the severity of rheumatic fever increases. We have, hence, found nothing peculiar in the immunologic response of

rheumatic fever subjects to infection with the hemolytic streptococcus. It would seem that such infections are important secondary factors, but not the actual cause of rheumatic fever.

Regarding the possible virus etiology of rheumatic fever, it is difficult to state much that is positive. It is no new theory. Several reports were in the literature as long as twenty years ago, but the claims were not substantiated. Two reports have more recently appeared from England, indicating that virus-like bodies may be obtained by high speed centrifugation in the pleural and pericardial exudates of rheumatic fever patients. These bodies appear by dark-field visualization to be similar to elementary bodies of known virus diseases. They were reported as being specifically agglutinated by serum from rheumatic fever patients, and in the last article cross agglutination was reported between rheumatic fever, rheumatoid arthritis, and chorea. Many technical difficulties present themselves with regard to this agglutination, and the work has not yet been corroborated. Several workers have tried, but have not yet recorded their disagreement. The specificity and the importance of such agglutination tests has been challenged by some virus workers. Before accepting any definite etiology, the disease must be reproduced in animals. We have had suggestive results in animals, but not conclusive ones. With new technical methods now available in the study of virus diseases, it is possible to study thoroughly the question. It would seem to me that this is distinctly indicated at present.

DR. J. B. STONE (RICHMOND, VA.).—To what degree should rheumatic patients be restricted after manifest signs and symptoms of active infection have disappeared?

CHAIRMAN JONES.—We make no differentiation concerning the length of bed care given patients with, and those without, evidence of rheumatic heart disease. The patient without previous evidence of rheumatic heart disease is just as likely to die of an attack of fulminating rheumatic fever as the patient with some degree of previous rheumatic heart disease. We attempt in so far as possible to give bed care so long as rheumatic fever is active, by either clinical symptoms or laboratory tests. This is not always possible to attain, but it is our general rule.

With the cessation of active rheumatic fever, the child is very slowly returned to activity, and there should be a long rest period after lunch over a period of months or even a year or two. After a suitable period of time without evidence of active rheumatic fever, the child is encouraged to be physically active. The majority of children are capable of even competitive exercise. Those with moderate to severe rheumatic heart disease will have some decrease in cardiac reserve, and rarely have to be told to limit their activity.

DR. J. B. MURPHY (SAN MATEO, CALIF.).—How long do you consider that the sedimentation rate should be normal before allowing a rheumatic patient out of bed? Of what significance are nosebleeds in themselves?

CHAIRMAN JONES.—The duration of rheumatic fever is usually so long and the child is given bed care for such a long period that a normal sedimentation rate, in the absence of clinical or other laboratory evidence of rheumatic fever, would be considered sufficient to warrant getting the patient out of bed.

Nontraumatic nosebleeds in the absence of other manifestations of rheumatic fever would not be considered sufficient to make a diagnosis of rheumatic fever. In the presence of rheumatic fever or rheumatic heart disease, they would be considered evidence of active rheumatic fever, usually corroborated by other findings.

DR. P. F. DWAN (MINNEAPOLIS, MINN.).—What do you consider the physical signs of active carditis?

DR. KING.—A persistently elevated pulse rate during sleep, a pericardial rub, the development of murmurs, and the evidence of congestive failure are the most helpful signs. A disturbance of conduction shown by the electrocardiogram should be emphasized as the most positive sign of carditis.

DR. E. MOODY (Los Angeles, Calif.).—Of what value is the x-ray in rheumatic heart disease?

DR. SHAPIRO.—X-ray studies including fluoroscopy are important in making an early diagnosis of rheumatic heart disease. Oblique as well as lateral and postero-anterior views are of value in ruling out early cardiac enlargement. However, it takes considerable experience in cardiac roentgenology before accurate conclusions can be drawn. Attempts to make a diagnosis on x-ray studies alone will surely lead to errors.

DR. A. C. BOST (San Francisco, Calif.).—Would Dr. King mention in what manner he measures a patient's exercise tolerance?

DR. KING.—There is no standardized method of determining exercise tolerance. Each patient presents a different problem. The history of his fatigability in light of his previous experience and in comparison with other children is probably the most reliable index. Repeated determinations of the vital capacity and his ability to perform uniform tests such as climbing stairs may be helpful.

DR. STONE.—What constitutes a normal temperature?

CHAIRMAN JONES.—We have considered a rectal temperature as normal when it does not exceed 100° F.

DR. C. M. MYERS (Oakland, Calif.).—What is the importance of abdominal symptoms in rheumatic subjects?

DR. KING.—Abdominal pain frequently occurs in patients with rheumatic fever and often preceding recrudescences of the disease. The location, nature, and severity of the pain are variable. It may or may not be associated with nausea and vomiting; it may simulate appendicitis and therefore create an important problem in differential diagnosis. Unnecessary laparotomy has been performed on many occasions. Abdominal pain in a rheumatic subject should arouse suspicion of activity of the disease.

DR. H. HOPKINS (Los Angeles, Calif.).—Can a differential line be drawn between polyarthritis and "further joint pains"?

DR. SHAPIRO.—Actually there is no difference between polyarthritis and "further joint pains." I tried to point out that many patients who had apparently recovered from a major attack of polyarthritis continued to "further joint pains," and that the presence of these pains should be taken as indicative of persistent active rheumatic infection.

DR. J. W. ROSENFELD (Portland, Ore.).—May not lower leg pains occurring in young and active children during periods of rest be the result of antecedent arch or muscle strain, and not the expression of an acute rheumatic infection?

CHAIRMAN JONES.—As pointed out by Dr. Shapiro, the joint symptoms of rheumatic fever usually are indicative of a definite arthralgia. Vague symptoms may occur, but with them there are usually other evidences of active rheumatic fever. Such symptoms as you describe in the presence of normal laboratory studies would not seem very indicative of rheumatic fever.

DR. DWAN.—I would like to stress the importance of local treatment of rheumatic joints. Children with painful joints will lie in bed with flexed joints until actual orthopedic problems appear due to muscle contraction.

DR. H. G. PONCHER (CHICAGO, ILL.).—Do you consider digitalization by the Eggleston method indicated in patients with rheumatic carditis during the acute phase of their disease? Is intravenous glucose of value during this stage?

DR. SHAPIRO.—Digitalization in active rheumatic fever is indicated only when there is evidence of cardiac decompensation. I do not use the Eggleston method but prefer to estimate the amount of digitalis necessary in each individual case depending on the grade of decompensation. Patients with active carditis with decompensation are hard to control with digitalis. It is difficult to determine the required amount of digitalis, and toxic symptoms occur quite commonly. It is a serious question whether or not digitalis does any good in this type of case. When digitalis does not produce the usual action in a patient with rheumatic heart disease, active carditis should be suspected.

Intravenous glucose may have some value in rheumatic fever. I have not used it much.

CHAIRMAN JONES.—We have been interested in the question of glucose therapy at the time of congestive failure. At times it has seemed helpful and would appear to be logical. Glycogen exhaustion would suggest its value. The severe liver changes in fatal cases would also make it appear to be logical. Further the severely ill rheumatic fever subject will rarely take sufficient nutrition, and glucose would hence supply necessary food.

DR. S. H. ASHMUN (DAYTON, OHIO).—In certain cases of rheumatic heart disease, may not tonsillectomy be indicated even in the absence of enlarged tonsils?

CHAIRMAN JONES.—We have been impressed with the frequency with which the bacterial findings of tonsils after removal are similar, regardless of their appearance while in the throat. I do not believe it possible by simple inspection of the tonsils to tell that they need to be removed, save in those cases of large tonsils which become obstructive during acute infection.

DR. B. P. STORTS (TUCSON, ARIZ.).—Of what value is fever therapy in chorea and rheumatic fever?

DR. SHAPIRO.—I have had no personal experience with fever therapy in chorea. Favorable results have been reported in the literature. The cases I have seen have not been sufficiently severe to warrant such drastic therapy. Although their course may be protracted, the disease is usually mild and always disappears eventually without specific treatment.

Fever treatment has been unsuccessful in rheumatic fever, and I do not use it.

CHAIRMAN JONES.—Dr. Shapiro's point is well taken. Exhaustive chorea is rarely seen today, and chorea is often a very chronic but mild manifestation of rheumatic fever, and one with a good outlook. It would seem unwarranted to use very frequently such a strenuous form of treatment. It is effective when used in rather violent chorea.

DR. W. W. QUILLIAN (MIAMI, FLA.).—Will you discuss further the effect upon rheumatic children of transportation to a subtropical environment?

DR. SHAPIRO.—As Dr. Jones reported at the last meeting of the American Rheumatism Association, he now feels that moving children with rheumatic fever to Florida is not warranted. He has shown that some of his patients who were transported from Boston to Miami continued to suffer from active rheumatic infection, and even fatal rheumatic disease occurred. I do not believe the question has been satisfactorily answered. It will be necessary first to determine the optimum locality in the southern part of the United States and then to carry on at least a five-year period of observation on rheumatic subjects transported there before drawing more definite conclusions. At the moment climatic change for rheumatic subjects does not appear warranted, especially wherein it entails economic sacrifice.

CHAIRMAN JONES.—I should like to add a few words to Dr. Shapiro's remarks. Under the conditions of the experiment in transporting rheumatic fever subjects to Florida, which he mentioned, the results were not entirely satisfactory. There was great annual variation, and recurrent rheumatic fever did occur spontaneously and after respiratory infection, without the hemolytic streptococcus as a secondary agent. There was a fatal recurrence in one instance. Respiratory infection is common in Florida, although hemolytic streptococcus infection is rarer. Transportation so far as we now know is not a panacea and should not be resorted to unless the family can well afford to stand the financial burden. Further it would be wise to keep the child away from the tourist centers and plan to leave him in the southern climate for four or five years.

We know but little of the results of transportation to an actual tropical climate. Rheumatic fever does occur in some tropical climates. The disease must be treated, in the main, in the climate where it originates. There is no reason why areas considered satisfactory for transportation should assume the financial responsibility of impecunious patients from other areas. I believe we could learn much from the many unfortunate happenings in sending tuberculous patients to far distant locations.

I should like to ask Dr. Tappan if she would not tell us her experience with rheumatic fever patients sent to Arizona.

DR. VIVIAN TAPPAN (TUCSON, ARIZ.).—It is difficult to give statistical evidences on the therapeutic results attained by transportation of rheumatic children to Arizona, first, because the rheumatic manifestations on arrival have varied so much, and second, because the periods of follow-up after leaving have been too brief to warrant drawing conclusions. In my experience, however, children with rheumatic infection tend to do well in Tucson. The degree of rheumatic activity on arrival has served as a more significant differentiating prognostic criterion than either the severity of past rheumatic infections, or the extent of endocardial damage. Progressive rheumatic infection has been seen in the transported group on rare occasions, but thus far has been limited to those who arrive in the acute phase of the disease and subsequently fail to reach a quiescent stage of their infection. Only transient exacerbations of the rheumatic state have been observed in patients with moderate or mild activity on arrival, and then restricted to the first weeks of their stay. Cases quiescent on reaching Tucson have remained so throughout their sojourn with a single exception. Thus one important therapeutic rationale for transportation to Arizona is found in the extraordinarily low incidence of rheumatic recurrences in this area, although it is well recognized that an exceptional case of primary rheumatic fever may be found in the native population, whether white or Indian.

There are no accurate means of gauging whether an active rheumatic infection clears more rapidly in Arizona. The lessened likelihood of severe respiratory infections, and the extreme improbability of a superimposed rheumatic infection are indirect factors pointing towards an accelerated convalescence. It has been suggested that the rheumatic infection is shorter lived under conditions of tropical heat, but this experiment, other factors being kept constant, has never been made —such for example as placing a patient in a "greenhouse" at home but allowing outside contacts.

I should like to say a word about upper respiratory infections and the incidence of beta hemolytic streptococci in Tucson. "Colds" are not at all uncommon, but they tend to be less severe and of shorter duration than in the East. The prevalence of hemolytic streptococci is extremely low as measured by repeated nasopharyngeal cultures taken on all types of patients with or without an associated respiratory infection a few weeks after their arrival in Arizona.

Finally, I must agree, although reluctantly, with the advice given by Dr. Jones not to transport children of the underprivileged classes to Arizona. Unless a rheu-

matic child can be kept away from the crowded health corridors of cheap tourist accommodations and unless necessary hospital and convalescent care can be given when indicated, he is better off at home. No adequate medical provision exists in the state for the care of the transient indigent sick. But if a satisfactory environment can be provided in a tropical or subtropical climate for rheumatic children, then I believe that transportation for long periods of time constitutes the therapeutic method of choice towards a lessening of progressive rheumatic disease. Certainly one wishes that long term experiments such as suggested by Dr. Jones and Dr. Shapiro could be undertaken to establish the truth or falseness of this concept.

CHAIRMAN JONES.—Would some one from the west coast like to express an opinion on the results of transportation to his state?

DR. L. MOON (SEATTLE, WASH.).—May not areas at present characterized by a low incidence of rheumatic fever develop in the future increasing percentages of primary rheumatic infections, as transportation of rheumatic patients continues? This has been the story of tuberculosis along the Pacific seaboard.

DR. RITA HOUGH (SAN DIEGO, CALIF.).—What educational measures should be instituted for the rheumatic child so as to minimize the development of psychiatric and social handicaps?

DR. SHAPIRO.—In Minneapolis we have a convalescent ward of forty beds in Lymanhurst as well as an outpatient cardiac clinic for children, a cooperative effort on the part of the Board of Education and the Board of Health. Two additional schools have been opened for the special care of rheumatic children during the quiescent phase of their disease. Bedside teaching is provided in the hospital for those children too ill to attend classes. In this manner loss of schooling over long periods of time is avoided. With the high school age group every attempt is made to offer them vocational training. After the acute rheumatic process has ceased, we do not feel there is reason for restricting the child unless the heart is seriously damaged. Children with far advanced heart disease will usually restrict themselves.

CHAIRMAN JONES.—As Dr. Shapiro indicates, we have little difficulty since we insist on a good deal of activity save when rheumatic fever is active, and at that time the child would not wish to play. When rheumatic heart disease is severe, the child must be taught to accept his limitations.

There is much confusion at present about what constitutes hospital care as opposed to convalescent care. In the ideal program for the care of the rheumatic child, there should be ample beds in the general or children's hospital for the acutely ill patients or for emergencies, these to be removed as soon as possible to a chronic hospital where long bed care may be obtained. Because of the recurring nature of rheumatic fever, it is impossible to have such an institution very far removed from the center which the institution serves. Following this, convalescent care begins and may be given at a more remote place. This type of care is different from that given in institutions giving long bed care during active rheumatic fever. After discharge from the place of convalescence good follow-up observation should be available. It is wise that the medical observation should be the same throughout the various phases of treatment, and, just as in tuberculosis, those give the best care who have learned the disease by living with it.

In conclusion, I should like to thank you for your sustained interest and attention. Thank you also for the freeness with which you have participated in the discussion.

DR. VIVIAN TAPPAN,
Tucson, Ariz.

Academy News

Dr. William Willey Jones has been appointed state chairman for Colorado, and Dr. Lemuel R. Brigman, state chairman for Nevada.

The Ninth Annual Meeting of the Academy will be held at the Netherland-Plaza Hotel, Cincinnati, Ohio, Nov. 16, 17, and 18, 1939.

The Region I meeting will be held at the Waldorf-Astoria Hotel in New York on June 1, 2, and 3, 1939; and the Region II meeting, May 15 and 16, 1939, at Memphis, Tenn.

News and Notes

At the close of a campaign for endowment and building funds for the **Rochester Academy of Medicine**, the Board of Trustees recently created the Albert David Kaiser Medal. This medal may be awarded annually, at the discretion of the Board of Trustees, to any fellow of the Rochester Academy of Medicine who has

(1) made any contribution of extraordinary merit to Medical Science or Public Health;

(2) performed some notable service for the benefit of the Medical profession; or

(3) distinguished himself in any manner, not necessarily connected with medicine, which has earned the recognition and approval of the community and of his colleagues in the Academy.

It was further resolved that the first award of the Albert David Kaiser Medal be made to Albert David Kaiser in recognition of his vision, leadership, and success, as chairman of the Endowment Fund Committee. The medal was presented to Dr. Kaiser by the president of the Academy of Medicine, Dr. David B. Jewett, at the first meeting in the new Academy home, Wednesday, Jan. 11, 1939.

Book Review

Nutrition: The Newer Diagnostic Methods. MILBANK MEMORIAL FUND, New York, 1938, pp. 192. Paper. Price $1.00.

This volume presents the proceedings of the Round Table on Nutrition held at the sixteenth Annual Conference of The Milbank Fund, March, 1938. It contains an excellent series of papers and discussions on modern diagnostic methods in the field of nutrition and their evaluation. The use of roentgenology in assessing the nutritional state is presented by the late Dr. T. Wingate Todd. "Dark adaptation" and the use of the photometer in the diagnosis of avitaminosis A are discussed by Hecht and Feldman, respectively. Soma Weiss discusses electrocardiography in the detection of B_1 deficiency and Levine and Marple's color tests for the same condition. Spies presents nicotinic acid, and Farmer and Abt discuss avitaminosis C. Hematologic methods in detecting nutritional anemia are presented by Guest, and plasma proteins in nutritional edema by Youmans. In addition, the discussion of the various topics by others in attendance who have been working in these fields, as Cullen, Peters, Ralli, Stuart, and Tisdall, is given.

It forms an excellent group of papers on timely and important subjects in which so much of our knowledge is dependent upon methods and their reliability.

The make-up of the book—printing, charts and graphs—is excellent and the Milbank Memorial Fund has rendered an excellent service, not only in holding the conference, but in making the proceedings available to the medical profession.

Errata

In the article, "Hypergenitalism in Children," by I. P. Bronstein, M.D., Chicago, Ill., which appeared in the February issue of the Journal, the following corrections should be noted:

On page 206 the last two lines of the first column of the footnote should read:

"Pubis to sole: 77 cm." and

"Pubis to vertex: 77 cm."

On page 208, under "Comment" the second sentence of the second paragraph should read,

"The negative results after repeated abdominal examinations, normal visualization of the *urinary* tract, and the absence of calcification in the kidney area argue against adrenal pathology (perirenal air administration was not attempted)."

On page 209, line 8, omit sentence,

"It is to be emphasized that precocious puberty is not caused by pituitary basophilism."

Comments

MAY DAY—CHILD HEALTH DAY, 1939

"The health of the child is the power of the nation." This slogan has been chosen for May Day—Child Health Day for 1939. The proclamation of May Day as Child Health Day by the President of the United States was authorized by congressional resolution in 1928, and it has become an important event in the development of child health activities. In each state May Day chairmen and committees are appointed by state health officers, and these in cooperation with departments of education formulate the local program.

The objectives of this year's program are to bring to the attention of each community:

> The importance to the child's health, development, and well-being throughout life, of proper food, rest, exercise, medical care, and protection against disease.
> The ways of informing parents and others how child health may be safeguarded, and
> The means whereby such safeguards may be made available for all children.

Emphasis in 1939 in the general program, as suggested by the Children's Bureau, is being placed on nutrition, and more specifically, "What is your community doing to promote good nutrition of mothers and children?" The Bureau has prepared an outline for submission to the local committees as an aid in surveying what is being done, what efforts are most effective, and what are the most outstanding shortcomings in the community activities which relate to nutrition. The emphasis this year on nutrition is one that calls for the technical help of physicians. Pediatricians will be asked to help and should help in every way with local Child Health Day activities. The program in the different states and communities will necessarily vary according to local needs, conditions, and resources. The state organizations of the Academy of Pediatrics should cooperate in every way with the state health officers and local committees in order that the local programs may be developed in a sound constructive way.